PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 239/94, A61K 31/505, C07D 401/04, 403/04, 405/04, 407/04, 409/04, 411/04, 413/14, 409/12, 411/12, 403/12, 401/12, 407/12, 409/14

A1

(11) International Publication Number: WO 97/30034

(43) International Publication Date: 21 August 1997 (21.08.97)

(21) International Application Number: PCT/GB97/00344

(22) International Filing Date: 10 February 1997 (10.02.97)

(30) Priority Data:
9603095.2 14 February 1996 (14.02.96) GB

(71) Applicant: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors: BARKER, Andrew, John; Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JOHNSTONE, Craig; Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: TAIT, Brian, Steele; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

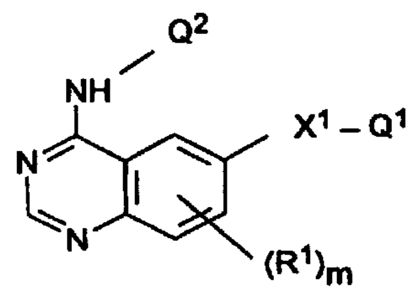
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS

(57) Abstract

The invention concerns quinazoline derivatives of formula (I), wherein X^1 is a direct link or a group such as CO, $C(R^2)_2$ and $CH(OR^2)$; wherein Q^1 is phenyl, naphthyl or a 5- or 6-membered heteroaryl moiety and Q^1 optionally bears up to 3 substituents; wherein m is 1 or 2 and each R^1 may be a group such as hydrogen, halogeno and trifluoromethyl; and wherein Q^2 may be phenyl or a 9- or 10-membered bicyclic heterocyclic moiety and Q^2 optionally bears up to 3 substituents; or a pharmaceutically acceptable salt thereof; processes for their preparation, pharmaceutical compositions containing them and the use of their receptor tyrosine kinase inhibitory properties in the treatment of proliferative disease such as cancer.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS

The invention relates to quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-proliferative activity such as anti-cancer activity and are accordingly useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-proliferative agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, <u>Mutagenesis</u>, 1986, <u>1</u>, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. The growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden <u>et al</u>., <u>Ann. Rev. Biochem</u>., 1988, <u>57</u>, 443; Larsen <u>et al</u>. <u>Ann. Reports in Med. Chem.</u> 1989, Chpt. 13).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, <u>Advances in Cancer Research</u>, 1993, <u>60</u>, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, transforming growth factor α (TGFα), NEU, erbB, Xmrk, DER and

let23 receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin, IGFI and insulin-related receptor (IRR) receptors and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors. It is known that Class I kinases such as the EGF family of receptor tyrosine kinases are frequently present in common human cancers such as breast cancer (Sainsbury et al., Brit. J. Cancer, 1988, 58, 458; Guerin et al., Oncogene Res., 1988, 3, 21 and Klijn et al., Breast Cancer Res. Treat., 1994, 29, 73), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny et al., Brit. J. Cancer, 1986, 54, 265; Reubi et al., Int. J. Cancer, 1990, 45, 269 and Rusch et al., Cancer Research, 1993, 53, 2379) and squamous cell cancer of the lung (Hendler et al., Cancer Cells, 1989, 7, 347), bladder cancer (Neal et al., Lancet, 1985, 366), oesophageal cancer (Mukaida et al., Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen et al., Oncogene Res., 1987, 1, 149), cancer of the prostate (Visakorpi et al., Histochem. J., 1992, 24, 481), leukaemia (Konaka et al., Cell, 1984, 37, 1035) and ovarian, bronchial or pancreatic cancer (European Patent Specification No. 0400586). As further human tumour tissues are tested for the EGF family of receptor tyrosine kinases it is expected that its widespread prevalance will be established in further cancers such as thyroid and uterine cancer. It is also known that EGF type tyrosine kinase activity is rarely detected in normal cells whereas it is more frequently detectable in malignant cells (Hunter, Cell, 1987, 50, 823). It has been shown more recently (W J Gullick, Brit. Med. Bull., 1991, 47, 87) that EGF receptors which possesses tyrosine kinase activity are overexpressed in many human cancers such as brain, lung squamous cell, bladder, gastric, colorectal, breast, head and neck, oesophageal, gynaecological and thyroid tumours.

Accordingly it has been recognised that an inhibitor of receptor tyrosine kinases should be of value as a selective inhibitor of the growth of mammalian cancer cells (Yaish et al. Science, 1988, 242, 933). Support for this view is provided by the demonstration that erbstatin, an EGF receptor tyrosine kinase inhibitor, specifically attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma which expresses EGF receptor tyrosine kinase but is without effect on the growth of another carcinoma which does not express EGF receptor tyrosine kinase (Toi et al., Eur. J. Cancer Clin. Oncol., 1990, 26, 722). Various derivatives of styrene are also stated to possess tyrosine kinase inhibitory

properties (European Patent Application Nos. 0211363, 0304493 and 0322738) and to be of use as anti-tumour agents. The in vivo inhibitory effect of two such styrene derivatives which are EGF receptor tyrosine kinase inhibitors has been demonstrated against the growth of human squamous cell carcinoma inoculated into nude mice (Yoneda et al., Cancer Research, 1991, 51, 4430). Accordingly it has been indicated that Class I receptor tyrosine kinase inhibitors will prove to be useful in the treatment of a variety of human cancers. Various known tyrosine kinase inhibitors are disclosed in a more recent review by T R Burke Jr. (Drugs of the Future, 1992, 17, 119).

EGF type receptor tyrosine kinases have also been implicated in non-malignant proliferative disorders such as psoriasis (Elder et al., Science, 1989, 243, 811). It is therefore expected that inhibitors of EGF type receptor tyrosine kinases will be useful in the treatment of non-malignant diseases of excessive cellular proliferation such as psoriasis (where TGFα is believed to be the most important growth factor) and benign prostatic hypertrophy (BPH), atherosclerosis and restenosis.

It is known from European Patent Applications Nos. 0520722 and 0566226 and from International Patent Applications WO 95/15758, WO 95/19169, WO 96/09294, WO 96/15118, WO 96/16960 and WO 96/30347 that certain quinazoline derivatives which bear an anilino substituent at the 4-position possess receptor tyrosine kinase inhibitory activity. It is further known from European Patent Application No. 0602851 and from International Patent Application WO 95/23141 that certain quinazoline derivatives which bear a heteroarylamino substituent at the 4-position also possess receptor tyrosine kinase inhibitory activity.

It is further known from International Patent Application WO 92/20642 that certain aryl and heteroaryl compounds inhibit EGF and/or PDGF receptor tyrosine kinase. There is the disclosure of certain quinazoline derivatives therein but no mention is made of 4-anilinoquinazoline derivatives.

It is further known from European Patent Application No. 0635507 and from International Patent Applications WO 95/06648, WO 95/19970 and WO 96/29331 that certain tricyclic compounds which comprise a 5- or 6-membered ring fused to the benzo-ring of a quinazoline possess receptor tyrosine kinase inhibitory activity or phosphodiesterase inhibitory activity. It is also known from European Patent Application No. 0635498 that

certain quinazoline derivatives which carry an amino group at the 6-position and a halogeno group at the 7-position possess receptor tyrosine kinase inhibitory activity.

The in vitro anti-proliferative effect of a 4-anilinoquinazoline derivative has been disclosed by Fry et al., Science, 1994, 265, 1093. It was stated that the compound 4-(3-bromoanilino)-6,7-dimethoxyquinazoline was a highly potent inhibitor of EGF receptor tyrosine kinase.

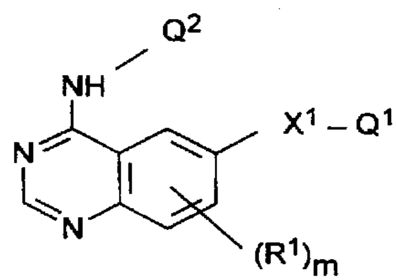
The in vivo inhibitory effect of a 4,5-dianilinophthalimide derivative which is an inhibitor of the EGF family of receptor tyrosine kinases has been demonstrated against the growth in BALB/c nude mice of a human epidermoid carcinoma A-431 or of a human ovarian carcinoma SKOV-3 (Buchdunger et al., Proc. Nat. Acad. Sci., 1994, 91, 2334).

It is further disclosed in International Patent Applications WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980 and WO 96/33981 that certain further quinazoline derivatives which bear an anilino substituent at the 4-position possess receptor tyrosine kinase inhibitory activity.

There is no disclosure in these documents of quinazoline derivatives which bear a heteroaryl moiety attached directly to the 6-position (other than the disclosure in International Patent Application WO 96/16960 of certain 4-anilinoquinazolines which bear a 5- or 9-membered nitrogen-linked heteroaryl moiety at the 6-position) or attached to the 6-position by way of a 1- or 2-atom chain, or of an aryl moiety attached directly to the 6-position or attached to the 6-position by way of a 1- or 2-atom chain [other than the disclosure in European Patent Application No. 0566226 of certain 4-anilinoquinazolines which bear an aryl moiety attached to the 6-position by way of a CONH, $NHCH_2$, CH_2NH or SCH_2 linking chain (with the aryl moiety attached to the first atom of these 2 atom linking groups, for example the carbon atom within the CONH group)].

We have now found that such compounds possess anti-proliferative properties which are believed to arise from their Class I (EGF type) receptor tyrosine kinase inhibitory activity.

According to the invention there is provided a quinazoline derivative of the formula I



I

wherein X^1 is a direct link or a group of the formula CO, $C(R^2)_2$, $CH(OR^2)$, $C(R^2)_2$-$C(R^2)_2$, $C(R^2)$=$C(R^2)$, C≡C, CH(CN), O, S, SO, SO_2, $N(R^2)$, $CON(R^2)$, $SO_2N(R^2)$, $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)$, $SC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2O$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$, and each R^2 is independently hydrogen or (1-4C)alkyl;

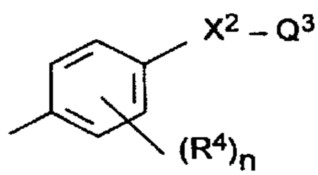
wherein Q^1 is phenyl, naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and Q^1 optionally bears up to 3 substituents selected from halogeno, hydroxy, amino, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-3C)alkylenedioxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(1-4C)alkylpiperazin-1-yl, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl, 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl, halogeno-(2-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-4C)alkoxy-(2-4C)alkoxy, amino-(2-4C)alkoxy, (1-4C)alkylamino-(2-4C)alkoxy, di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, (1-4C)alkylthio-(2-4C)alkoxy, (1-4C)alkylsulphinyl-(2-4C)alkoxy, (1-4C)alkylsulphonyl-(2-4C)alkoxy, halogeno-(2-4C)alkylamino, hydroxy-(2-4C)alkylamino, (1-4C)alkoxy-(2-4C)alkylamino, amino-(2-4C)alkylamino, (1-4C)alkylamino-(2-4C)alkylamino, di-[(1-4C)alkyl]amino-(2-4C)alkylamino, pyrrolidin-1-yl-(2-4C)alkylamino, piperidino-(2-4C)alkylamino,

morpholino-(2-4C)alkylamino, piperazin-1-yl-(2-4C)alkylamino, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkylamino, N-(1-4C)alkyl-halogeno-(2-4C)alkylamino, N-(1-4C)alkyl-hydroxy-(2-4C)alkylamino, N-(1-4C)alkyl-(1-4C)alkoxy-(2-4C)alkylamino, halogeno-(2-4C)alkanoylamino, hydroxy-(2-4C)alkanoylamino, (1-4C)alkoxy-(2-4C)alkanoylamino, (3-4C)alkenoylamino, (3-4C)alkynoylamino, amino-(2-4C)alkanoylamino, (1-4C)alkylamino-(2-4C)alkanoylamino, di-[(1-4C)alkyl]amino-(2-4C)alkanoylamino, pyrrolidin-1-yl-(2-4C)alkanoylamino, piperidino-(2-4C)alkanoylamino, morpholino-(2-4C)alkanoylamino, piperazin-1-yl-(2-4C)alkanoylamino and 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkanoylamino, and wherein any of the above-mentioned substituents comprising a CH_2 (methylene) group which is not attached to a halogeno, SO or SO_2 group or to a N, O or S atom optionally bears on said CH_2 group a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

wherein m is 1 or 2 and each R^1 is independently hydrogen, halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-4C)alkoxycarbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl or N,N-di-[(1-4C)alkyl]carbamoyl;

and wherein Q^2 is phenyl or a 9- or 10-membered bicyclic heterocyclic moiety containing 1 or 2 nitrogen heteroatoms and optionally containing a further heteroatom selected from oxygen, nitrogen and sulphur, and Q^2 optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-(1-4C)alkylcarbamoyl,

or Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula CO, $C(R^3)_2$, $CH(OR^3)$, $C(R^3)_2$-$C(R^3)_2$, $C(R^3)$=$C(R^3)$, C≡C, CH(CN), O, S, SO, SO_2, $N(R^3)$, $CON(R^3)$, $SO_2N(R^3)$, $N(R^3)CO$, $N(R^3)SO_2$, $OC(R^3)_2$, $SC(R^3)_2$, $C(R^3)_2O$ or $C(R^3)_2S$ wherein each R^3 is independently hydrogen or (1-4C)alkyl,

Q^3 is phenyl or naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heteroaryl moiety is a single ring or is fused to a benzo ring, and wherein said phenyl or naphthyl group or heteroaryl moiety optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-[(1-4C)alkyl]carbamoyl,

n is 1, 2 or 3 and each R^4 is independently hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino or (2-4C)alkanoylamino;

or a pharmaceutically-acceptable salt thereof;

provided that, when Q^1 is optionally-substituted phenyl, X^1 is not $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$; and when X^1 is a direct link, Q^1 is not a 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to 3 nitrogen heteroatoms.

According to a further aspect of the invention there is provided a quinazoline derivative of the formula I

wherein X^1 is a direct link or a group of the formula CO, $C(R^2)_2$, $CH(OR^2)$, $C(R^2)_2$-$C(R^2)_2$, $C(R^2)$=$C(R^2)$, C≡C, CH(CN), O, S, SO, SO_2, $N(R^2)$, $CON(R^2)$, $SO_2N(R^2)$, $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)_2$, $SC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2O$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$, and each R^2 is independently hydrogen or (1-4C)alkyl;

wherein Q^1 is a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and Q^1 optionally bears up to 3 substituents selected from halogeno, hydroxy, amino, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-3C)alkylenedioxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(1-4C)alkylpiperazin-1-yl, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl,

piperazin-1-yl-(1-4C)alkyl, 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl, halogeno-(2-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-4C)alkoxy-(2-4C)alkoxy, amino-(2-4C)alkoxy, (1-4C)alkylamino-(2-4C)alkoxy, di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, (1-4C)alkylthio-(2-4C)alkoxy, (1-4C)alkylsulphinyl-(2-4C)alkoxy, (1-4C)alkylsulphonyl-(2-4C)alkoxy, halogeno-(2-4C)alkylamino, hydroxy-(2-4C)alkylamino, (1-4C)alkoxy-(2-4C)alkylamino, amino-(2-4C)alkylamino, (1-4C)alkylamino-(2-4C)alkylamino, di-[(1-4C)alkyl]amino-(2-4C)alkylamino, pyrrolidin-1-yl-(2-4C)alkylamino, piperidino-(2-4C)alkylamino, morpholino-(2-4C)alkylamino, piperazin-1-yl-(2-4C)alkylamino, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkylamino, N-(1-4C)alkyl-halogeno-(2-4C)alkylamino, N-(1-4C)alkyl-hydroxy-(2-4C)alkylamino, N-(1-4C)alkyl-(1-4C)alkoxy-(2-4C)alkylamino, halogeno-(2-4C)alkanoylamino, hydroxy-(2-4C)alkanoylamino, (1-4C)alkoxy-(2-4C)alkanoylamino, (3-4C)alkenoylamino, (3-4C)alkynoylamino, amino-(2-4C)alkanoylamino, (1-4C)alkylamino-(2-4C)alkanoylamino, di-[(1-4C)alkyl]amino-(2-4C)alkanoylamino, pyrrolidin-1-yl-(2-4C)alkanoylamino, piperidino-(2-4C)alkanoylamino, morpholino-(2-4C)alkanoylamino, piperazin-1-yl-(2-4C)alkanoylamino and 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkanoylamino, and wherein any of the above-mentioned substituents comprising a CH_2 (methylene) group which is not attached to a halogeno, SO or SO_2 group or to a N, O or S atom optionally bears on said CH_2 group a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

wherein m is 1 or 2 and each R^1 is independently hydrogen, halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-4C)alkoxycarbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl or N,N-di-[(1-4C)alkyl]carbamoyl;

and wherein Q^2 is phenyl which optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-(1-4C)alkylcarbamoyl;

or a pharmaceutically-acceptable salt thereof;

provided that, when X^1 is a direct link, Q^1 is not a 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to 3 nitrogen heteroatoms.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example when R^1 is a hydroxy-(2-4C)alkoxy group, suitable values for this generic radical include 2-hydroxyethoxy, 2-hydroxypropoxy, 1-hydroxyprop-2-yloxy and 3-hydroxypropoxy. An analogous convention applies to other generic terms.

Within the present invention it is to be understood that a quinazoline derivative of the formula I may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which possesses anti-proliferative activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

The quinazolines of the formula I are unsubstituted at the 2-position thus it is to be understood that the R^1 groups are located only on the benzo portion of the quinazoline ring.

It is also to be understood that certain quinazoline derivatives of the formula I can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess anti-proliferative activity.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for a substituent on Q^1, Q^2 or Q^3, for a substituent on a CH_2 group within a substituent on Q^1, or for R^1, R^2, R^3 or R^4 when it is halogeno is, for example, fluoro, chloro, bromo or iodo;

when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl or butyl;

when it is (1-4C)alkoxy is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy;

when it is (1-4C)alkylamino is, for example, methylamino, ethylamino or propylamino;

when it is di-[(1-4C)alkyl]amino is, for example, dimethylamino, diethylamino, N-ethyl-N-methylamino or dipropylamino;

when it is (2-4C)alkanoylamino is, for example, acetamido, propionamido or butyramido;

when it is (1-4C)alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxcarbonyl or tert-butoxycarbonyl;

when it is N-(1-4C)alkylcarbamoyl is, for example, N-methylcarbamoyl or N-ethylcarbamoyl;

and when it is N,N-di-[(1-4C)alkyl]carbamoyl is, for example, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl.

Suitable values for each substituent which may be present on Q^1 include, for example:-

for (2-4C)alkenyloxy:	vinyloxy and allyloxy;
for (2-4C)alkynyloxy:	2-propynyloxy;
for (1-3C)alkylenedioxy:	methylenedioxy, ethylenedioxy and propylenedioxy;
for 4-(1-4C)alkyl-piperazin-1-yl:	4-methylpiperazin-1-yl and 4-ethylpiperazin-1-yl;
for amino-(1-4C)alkyl:	aminomethyl, 2-aminoethyl and 3-aminopropyl;
for (1-4C)alkylamino-(1-4C)alkyl:	methylaminomethyl, 2-methylaminoethyl and 3-methylaminopropyl;
for di-[(1-4C)alkyl]amino-(1-4C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl and 3-dimethylaminopropyl;
for pyrrolidin-1-yl-(1-4C)alkyl:	pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl and 3-pyrrolidin-1-ylpropyl;
for piperidino-(1-4C)alkyl:	piperidinomethyl, 2-piperidinoethyl and 3-piperidinopropyl;
for morpholino-(1-4C)alkyl:	morpholinomethyl, 2-morpholinoethyl and 3-morpholinopropyl;
for piperazin-1-yl-(1-4C)alkyl:	piperazin-1-ylmethyl, 2-piperazin-1-ylethyl and 3-piperazin-1-ylpropyl;
for 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl:	4-methylpiperazin-1-ylmethyl, 2-(4-methylpiperazin-1-yl)ethyl and 3-(4-methylpiperazin-1-yl)propyl;
for halogeno-(2-4C)alkoxy:	2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 3-fluoropropoxy, 3-chloropropoxy, 2,2,2-trifluoroethoxy, 1,1,2,2,2-pentafluoroethoxy,

2,2,3,3-tetrafluoropropoxy, 2,2,3,3,3-pentafluoropropoxy and 1,1,2,2,3,3,3-heptafluoropropoxy;

for hydroxy-(2-4C)alkoxy:	2-hydroxyethoxy, 3-hydroxypropoxy and 4-hydroxybutoxy;
for (1-4C)alkoxy-(2-4C)alkoxy:	2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy and 3-ethoxypropoxy;
for amino-(2-4C)alkoxy:	2-aminoethoxy and 3-aminopropoxy;
for (1-4C)alkylamino-(2-4C)-alkoxy:	2-methylaminoethoxy, 2-ethylaminoethoxy, 2-propylaminoethoxy, 3-methylaminopropoxy and 3-ethylaminopropoxy;
for di-[(1-4C)alkyl]amino-(2-4C)alkoxy:	2-dimethylaminoethoxy, 2-(N-ethyl-N-methylamino)ethoxy, 2-diethylaminoethoxy, 2-dipropylaminoethoxy, 3-dimethylaminopropoxy and 3-diethylaminopropoxy;
for pyrrolidin-1-yl-(2-4C)-alkoxy:	2-(pyrrolidin-1-yl)ethoxy and 3-(pyrrolidin-1-yl)propoxy;
for piperidino-(2-4C)alkoxy:	2-piperidinoethoxy and 3-piperidinopropoxy;
for morpholino-(2-4C)alkoxy:	2-morpholinoethoxy and 3-morpholinopropoxy;
for piperazin-1-yl-(2-4C)alkoxy:	2-(piperazin-1-yl)ethoxy and 3-(piperazin-1-yl)propoxy;
for 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy:	2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;
for (1-4C)alkylthio-(2-4C)alkoxy:	2-methylthioethoxy and 3-methylthiopropoxy;
for (1-4C)alkylsulphinyl-(2-4C)-alkoxy:	2-methylsulphinylethoxy and 3-methylsulphinylpropoxy;

for (1-4C)alkylsulphonyl-(2-4C)-alkoxy:	2-methylsulphonylethoxy and 3-methylsulphonylpropoxy;
for halogeno-(2-4C)alkylamino:	2-fluoroethylamino, 2-chloroethylamino, 2-bromoethylamino, 3-fluoropropylamino and 3-chloropropylamino;
for hydroxy-(2-4C)alkylamino:	2-hydroxyethylamino, 3-hydroxypropylamino and 4-hydroxybutylamino;
for (1-4C)alkoxy-(2-4C)alkyl-amino:	2-methoxyethylamino, 2-ethoxyethylamino, 3-methoxypropylamino and 3-ethoxypropylamino;
for amino-(2-4C)alkylamino:	2-aminoethylamino, 3-aminopropylamino and 4-aminobutylamino;
for (1-4C)alkylamino-(2-4C)alkylamino:	2-methylaminoethylamino, 2-ethyl-aminoethylamino, 2-propylaminoethylamino, 3-methylaminopropylamino, 3-ethylaminopropylamino and 4-methylaminobutylamino;
for di-[(1-4C)alkyl]amino-(2-4C)alkylamino:	2-dimethylaminoethylamino, 2-(N-ethyl-N-methylamino)ethylamino, 2-diethylaminoethylamino, 2-dipropylaminoethylamino, 3-dimethylaminopropylamino, 3-diethylaminopropylamino and 4-dimethylaminobutylamino;
for pyrrolidin-1-yl-(2-4C)-alkylamino:	2-(pyrrolidin-1-yl)ethylamino and 3-(pyrrolidin-1-yl)propylamino;
for piperidino-(2-4C)alkylamino:	2-piperidinoethylamino and 3-piperidinopropylamino;

for morpholino-(2-4C)alkylamino: 2-morpholinoethylamino and 3-morpholinopropylamino;

for piperazin-1-yl-(2-4C)-alkylamino: 2-(piperazin-1-yl)ethylamino and 3-(piperazin-1-yl)propylamino;

for 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkylamino: 2-(4-methylpiperazin-1-yl)ethylamino and 3-(4-methylpiperazin-1-yl)propylamino;

for N-(1-4C)alkyl-halogeno-(2-4C)alkylamino: N-(2-chloroethyl)-N-methylamino, N-(2-bromoethyl)-N-methylamino and N-(2-bromoethyl)-N-ethylamino;

for N-(1-4C)alkyl-hydroxy-(2-4C)-alkylamino: N-(2-hydroxyethyl)-N-methylamino, N-(3-hydroxypropyl)-N-methylamino and N-ethyl-N-(2-hydroxyethyl)amino;

for N-(1-4C)alkyl-(1-4C)alkoxy-(2-4C)alkylamino: N-methyl-N-(2-methoxyethyl)amino, N-methyl-N-(3-methoxypropyl)amino and N-ethyl-N-(2-methoxyethyl)amino;

for halogeno-(2-4C)alkanoylamino: 2-chloroacetamido, 2-bromoacetamido, 3-chloropropionamido and 3-bromopropionamido;

for hydroxy-(2-4C)alkanoylamino: 2-hydroxyacetamido, 3-hydroxypropionamido and 4-hydroxybutyramido;

for (1-4C)alkoxy-(2-4C)-alkanoylamino: 2-methoxyacetamido, 2-ethoxyacetamido, 2-propoxyacetamido, 3-methoxypropionamido, 3-ethoxypropionamido and 4-methoxybutyramido;

for (3-4C)alkenoylamino: acrylamido, methacrylamido, crotonamido and isocrotonamido;

for (3-4C)alkynoylamino:	propiolamido;
for amino-(2-4C)alkanoylamino:	2-aminoacetamido, 2-aminopropionamido and 3-aminopropionamido;
for (1-4C)alkylamino-(2-4C)-alkanoylamino:	2-methylaminoacetamido, 2-ethylaminoacetamido, 2-methylaminopropionamido and 3-methylaminopropionamido;
for di-[(1-4C)alkyl]amino-(2-4C)-alkanoylamino:	2-dimethylaminoacetamido, 2-diethylaminoacetamido, 2-dimethylaminopropionamido and 3-dimethylaminopropionamido;
for pyrrolidin-1-yl-(2-4C)-alkanoylamino:	2-pyrrolidin-1-ylacetamido, 2-pyrrolidin-1-ylpropionamido and 3-pyrrolidin-1-ylpropionamido;
for piperidino-(2-4C)-alkanoylamino:	2-piperidinoacetamido, 2-piperidinopropionamido and 3-piperidinopropionamido;
for morpholino-(2-4C)-alkanoylamino:	2-morpholinoacetamido, 2-morpholinopropionamido and 3-morpholinopropionamido;
for piperazin-1-yl-(2-4C)-alkanoylamino:	2-piperazin-1-ylacetamido, 2-piperazin-1-ylpropionamido and 3-piperazin-1-ylpropionamido;
for 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkanoylamino:	2-(4-methylpiperazin-1-yl)acetamido, 2-(4-methylpiperazin-1-yl)propionamido and 3-(4-methylpiperazin-1-yl)propionamido.

When there is a (1-3C)alkylenedioxy substituted on Q^1, the oxygen atoms thereof occupy adjacent positions on the Q^1 ring.

When m is 1 the R^1 substituent is preferably located at the 7-position of the quinazoline ring.

Suitable substituents formed when any of the substituents on Q^1 comprising a CH_2 group which is not attached to a halogeno, SO or SO_2 group or to a N, O or S atom bears on said CH_2 group a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino include, for example, substituted (1-4C)alkylamino-(2-4C)alkoxy or di-[(1-4C)alkyl]amino-(2-4C)alkoxy groups, for example hydroxy-(1-4C)alkylamino-(2-4C)alkoxy or hydroxy-di-[(1-4C)alkyl]amino-(2-4C)alkoxy groups such as 3-methylamino-2-hydroxypropoxy and 3-dimethylamino-2-hydroxypropoxy.

A suitable value for Q^1 and Q^3 when it is a naphthyl group is, for example, 1-naphthyl or 2-naphthyl.

A suitable value for Q^1 or Q^3 when it is a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which is a single ring is, for example, furyl, pyrrolyl, thienyl, pyridyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl or thiadiazoylyl, or which is fused to a benzo ring is, for example, benzofuryl, indolyl, benzothienyl, quinolyl, isoquinolyl, benzoxazolyl, indazolyl, benzimidazolyl, benzothiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl or benzotriazolyl. Said heteroaryl moiety may be attached to X^1 and X^2 through any available position. The optional substituents on Q^1 or Q^3 may be located at any available position including on any available nitrogen heteroatom.

A suitable value for Q^2 when it is 9- or 10-membered bicyclic heterocyclic moiety containing 1 or 2 nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulphur is, for example, a benzo-fused heterocyclic moiety such as indolyl, isoindolyl, indolizinyl, 1H-benzimidazolyl, 1H-indazolyl, benzoxazolyl, benzo[c]isoxazolyl, benzo[d]isoxazolyl, benzothiazolyl, benzo[c]isothiazolyl, benzo[d]isothiazolyl, 1H-benzotriazolyl, benzo[c]furazanyl, benzo[c][2,1,3]thiadiazolyl, benzo[d][1,2,3]oxadiazolyl, benzo[d][1,2,3]thiadiazolyl, quinolyl, 1,2-dihydroquinolinyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 4H-1,4-benzoxazinyl or 4H-1,4-benzothiazinyl.

The heterocyclic moiety may be attached through any available position including from either of the two rings of the bicyclic heterocyclic moiety. The heterocyclic moiety may bear a suitable substituent such as a (1-4C)alkyl substituent on an available nitrogen atom.

It is also to be understood that, within the structure of formula I, when X^1 is, for example, a group of the formula $C(R^2)_2O$, it is the C atom which is attached to the quinazoline ring and the O atom which is attached to Q^1. Likewise, when X^2 is, for example, a group of the formula $N(R^3)SO_2$, it is the N atom which is attached to the phenylene ring and the SO_2 group which is attached to Q^3. Likewise, when X^1 is, for example, a group of the formula $CON(R^2)$, it is the CO group which is attached to the quinazoline ring and the N atom which is attached to Q^1.

A suitable pharmaceutically-acceptable salt of a quinazoline derivative of the invention is, for example, an acid-addition salt of a quinazoline derivative of the invention which is sufficiently basic, for example, a mono- or di-acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a quinazoline derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Q^1, X^1, m, R^1 and Q^2 has any of the meanings defined hereinbefore or in this section concerning particular compounds of the invention:-

(a) X^1 is a direct link;

(b) X^1 is a group of the formula CO, CH_2, CH(OH), CH_2CH_2, CH=CH, C≡C, O, S, SO, SO_2, NH, CONH, SO_2NH, NHCO, $NHSO_2$, OCH_2, SCH_2, $NHCH_2$, CH_2O, CH_2S or CH_2NH;

(c) X^1 is a group of the formula CH_2, CH_2CH_2, O, S, SO, SO_2, NH, NHCO, $NHSO_2$, OCH_2 or $NHCH_2$;

(d) Q^1 is phenyl optionally substituted as defined hereinbefore;

(e) Q^1 is a 5- or 6-membered monocyclic heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur which is optionally substituted as defined hereinbefore;

(f) Q^1 is furyl, pyrrolyl, thienyl, pyridyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,3-triazolyl or 1,2,4-triazolyl which is attached from any available position including from a nitrogen atom and which is optionally substituted as defined hereinbefore;

(g) Q^1 bears no optional substituents;

(h) Q^1 bears 1 or 2 substituents selected from halogeno, hydroxy, amino, trifluoromethoxy, trifluoromethyl, cyano, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino and (2-4C)alkanoylamino;

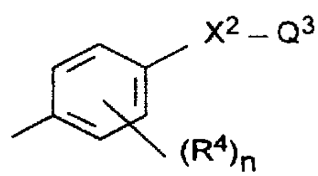
(i) Q^1 bears a substituent selected from amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl and 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl;

(j) m is 1 and R^1 is hydrogen;

(k) m is 1 and R^1 is (1-4C)alkoxy;

(l) Q^2 is phenyl which is optionally substituted as defined hereinbefore;

(m) Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula CO, CH_2, CH(OH), S, SO_2NH or OCH_2, Q^3 is phenyl or pyridyl which optionally bears 1 or 2 substituents selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy, n is 1 and R^4 is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy;

(n) Q^2 is a group of the formula II wherein X^2 is a group of the formula CO, Q^3 is phenyl which optionally bears 1 or 2 substituents selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy, n is 1 and R^4 is hydrogen, halogeno or (1-4C)alkyl; and

(o) Q^2 is a group of the formula II wherein X^2 is a group of the formula OCH_2, Q^3 is pyridyl, n is 1 and R^4 is hydrogen, halogeno or (1-4C)alkyl;

provided that when Q^1 is optionally-substituted phenyl, X^1 is not $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$; and when X^1 is a direct link, Q^1 is not a 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to 3 nitrogen heteroatoms.

A preferred compound of the invention is a quinazoline derivative of the formula I

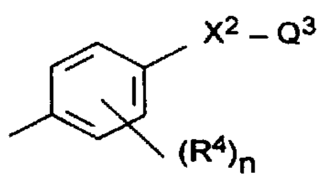
wherein X^1 is a direct link or a group of the formula CH_2, CH_2CH_2, NH, NHCO, $NHSO_2$, OCH_2, SCH_2, $NHCH_2$, CH_2O or CH_2S;

$Q^1$is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-isoxazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, 2-thiazolyl, 4-thiazolyl, 5-isothiazolyl or 1,2,3-triazol-4-yl which optionally bears a substituent selected from methyl, aminomethyl, 2-aminoethyl, methylaminomethyl, 2-methylaminoethyl, dimethylaminomethyl, 2-dimethylaminoethyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, piperidinomethyl, 2-piperidinoethyl, morpholinomethyl, 2-morpholinoethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 4-methylpiperazin-1-ylmethyl and 2-(4-methylpiperazin-1-yl)ethyl;

m is 1 and R^1 is hydrogen or methoxy;

and Q^2 is phenyl which optionally bears 1, 2 or 3 substituents selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl and methoxy,

or Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula CO or OCH_2, Q^3 is phenyl or 2-pyridyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo, methyl and methoxy, n is 1 and R^4 is hydrogen, fluoro, chloro, bromo or methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I

wherein X^1 is a direct link or a group of the formula NHCO, OCH_2 or $NHCH_2$;

Q^1 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-oxazolyl, 5-isoxazolyl or 4-imidazolyl which optionally bears a substituent selected from aminomethyl, morpholinomethyl and 2-morpholinoethyl;
m is 1 and R^1 is hydrogen or methoxy;
and Q^2 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo and methyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

A specific especially preferred compound of the invention is the quinazoline derivative of the formula I:-
4-(3-chloro-4-fluoroanilino)-6-(3-furyl)quinazoline,
4-(3-chloro-4-fluoroanilino)-6-(2-thienyl)quinazoline,
4-(3-chloro-4-fluoroanilino)-6-[5-(2-morpholinoethyl)thien-2-yl]quinazoline,
4-(3-chloro-4-fluoroanilino)-6-(5-morpholinomethylthien-3-yl)quinazoline or
4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-pyridylmethoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I
wherein X^1 is a direct link;
Q^1 is thienyl which bears a substituent selected from amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl and 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl;
m is 1 and R^1 is hydrogen;
and Q^2 is phenyl which optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-(1-4C)alkylcarbamoyl;
or a pharmaceutically-acceptable salt thereof.

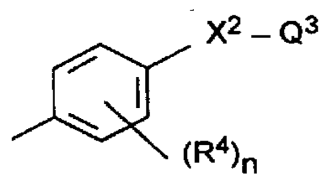
A further preferred compound of the invention is a quinazoline derivative of the formula I
wherein X^1 is a direct link;
Q^1 is 2-thienyl which optionally bears a substituent selected from methyl, aminomethyl,

2-aminoethyl, methylaminomethyl, 2-methylaminoethyl, dimethylaminomethyl, 2-dimethylaminoethyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, piperidinomethyl, 2-piperidinoethyl, morpholinomethyl, 2-morpholinoethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 4-methylpiperazin-1-ylmethyl and 2-(4-methylpiperazin-1-yl)ethyl;
m is 1 and R^1 is hydrogen or methoxy;
and Q^2 is phenyl which optionally bears 1, 2 or 3 substituents selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl and methoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I
wherein X^1 is a direct link;
Q^1 is 2-thienyl which optionally bears a substituent selected from aminomethyl, morpholinomethyl and 2-morpholinoethyl;
m is 1 and R^1 is hydrogen or methoxy;
and Q^2 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo and methyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific especially preferred compound of the invention is the quinazoline derivative of the formula I:-
4-(3-chloro-4-fluoroanilino)-6-[5-(2-morpholinoethyl)thien-2-yl]quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I wherein X^1 is a direct link or a group of the formula O;
Q^1 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo, amino, cyano, nitro, aminomethyl, methylaminomethyl, dimethylaminomethyl, diethylaminomethyl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl;
m is 1 and R^1 is hydrogen or methoxy; and
Q^2 is phenyl which optionally bears 1, 2 or 3 substituents selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl and methoxy,
or Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula OCH_2, Q^3 is 2-pyridyl, n is 1 and R^4 is hydrogen, fluoro, chloro or methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I wherein X^1 is a direct link or a group of the formula O;

Q^1 is phenyl which optionally bears 1 or 2 substituents selected from amino, aminomethyl, diethylaminomethyl, pyrrolidin-1-ylmethyl, piperidinomethyl and morpholinomethyl;

m is 1 and R^1 is hydrogen; and

Q^2 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro and methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific especially preferred compound of the invention is the quinazoline derivative of the formula I:-

4-(3-methylanilino)-6-phenylquinazoline,

6-(4-aminomethylphenyl)-4-(3-chloro-4-fluoroanilino)quinazoline,

6-(4-aminophenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline,

6-(4-aminomethylphenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline or

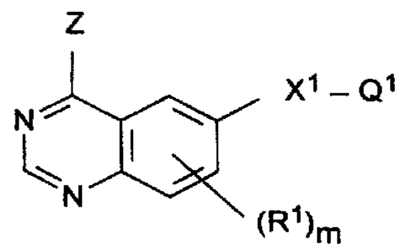
4-(3-chloro-4-fluoroanilino)-6-(4-morpholinomethylphenoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes include, for example, those illustrated in European Patent Applications Nos. 0520722, 0566226, 0602851, 0635507 and 0635498, and International Patent Applications WO 96/15118 and WO 96/16960. Such processes, when used to prepare a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, X^1, Q^1, m, R^1 and Q^2 have any of the meanings defined hereinbefore for a quinazoline derivative of the formula I. Necessary

starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) The reaction, conveniently in the presence of a suitable base, of a quinazoline of the formula III



III

wherein Z is a displaceable group, with an aniline of the formula Q^2-NH_2.

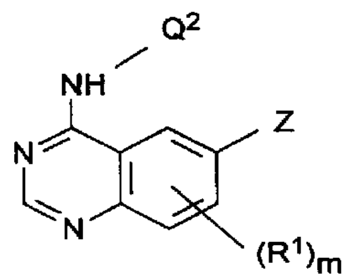
A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group Z is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 80°C.

The quinazoline derivative of the formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-Z wherein Z has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an

organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

(b) For the preparation of those compounds of the formula I wherein X^1 is a direct link, the reaction, conveniently in the presence of a suitable catalyst, of a quinazoline of the formula IV



IV

wherein Z is a displaceable group as defined hereinbefore, with an organoboron reagent of the formula Q^1-$B(L^1)(L^2)$ wherein each L^1 and L^2, which may be the same or different, is a suitable ligand.

A suitable value for the ligands L^1 and L^2 which are present on the boron atom include, for example, a hydroxy, (1-4C)alkoxy or (1-6C)alkyl ligand, for example a hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methyl, ethyl, propyl, isopropyl or butyl ligand. Alternatively the ligands L^1 and L^2 may be linked such that, together with the boron atom to which they are attached, they form a ring. For example, L^1 and L^2 together may define an oxy-(2-4C)alkylene-oxy group, for example an oxyethyleneoxy or oxytrimethyleneoxy group such that, together with the boron atom to which they are attached, they form a cyclic boronic acid ester group. Particularly suitable organoboron reagents include, for example, compounds of the formulae Q^1-$B(OH)_2$, Q^1-$B(OPr^i)_2$ and Q^1-$B(Et)_2$.

A suitable catalyst for the reaction includes, for example, a metallic catalyst such as a palladium(0), palladium(II), nickel(0) or nickel(II) catalyst, for example tetrakis(triphenylphosphine)palladium(0), palladium(II) chloride, palladium(II) bromide, bis(triphenylphosphine)palladium(II) chloride, tetrakis(triphenylphosphine)nickel(0), nickel(II) chloride, nickel(II) bromide or bis(triphenylphosphine)nickel(II) chloride. In

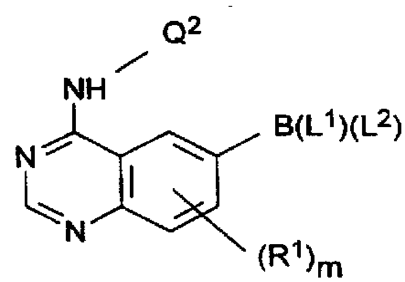
addition a free radical initiator may conveniently be added, for example an azo compound such as azo(bisisobutyronitrile).

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran, 1,4-dioxan or 1,2-dimethoxyethane, an aromatic solvent such as benzene, toluene or xylene, or an alcohol such as methanol or ethanol, and the reaction is conveniently carried out at a temperature in the range, for example 10 to 250°C, preferably in the range 60 to 120°C.

Organoboron reagents of the formula Q^1-B(L^1)(L^2) may be obtained by standard procedures of organic chemistry which are within the ordinary skill of an organic chemist, for example by the reaction of an organometallic compound of the formula Q^1-M, wherein M is, for example, lithium or the magnesium halide portion of a Grignard reagent, with an organoboron compound of the formula Z-B(L^1)(L^2) wherein Z is a displaceable group as defined hereinbefore. Preferably the compound of the formula Z-B(L^1)(L^2) is, for example, boric acid or a tri-(1-4C)alkyl borate such as tri-isopropyl borate.

In an alternative procedure the organoboron compound of the formula Q^1-B(L^1)(L^2) may be replaced with an organometallic compound of the formula Q^1-M wherein M is a metal atom or a metallic group (i.e. a metal atom bearing suitable ligands). Suitable values for the metal atom include, for example, lithium and copper. Suitable values for the metallic group include, for example, groups which contain a tin, silicon, zirconium, aluminium, magnesium or mercury atom. Suitable ligands within such a metallic group include, for example, hydroxy groups, (1-6C)alkyl groups such as methyl, ethyl, propyl, isopropyl and butyl groups, halogeno groups such as chloro, bromo and iodo groups, and (1-6C)alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy and butoxy groups. A particular organometallic compound of the formula Q^1-M is, for example, an organotin compound such as a compound of the formula Q^1-$SnBu_3$, an organosilicon compound such as a compound of the formula Q^1-Si(Me)F_2, an organozirconium compound such as a compound of the formula Q^1-$ZrCl_3$, an organoaluminium compound such as a compound of the formula Q^1-$AlEt_2$, an organomagnesium compound such as a compound of the formula Q^1-MgBr, or an organomercury compound such as a compound of the formula Q^1-HgBr.

(c) For the preparation of those compounds of the formula I wherein X^1 is a direct link, the reaction, conveniently in the presence of a suitable catalyst as defined hereinbefore, of a quinazoline of the formula V



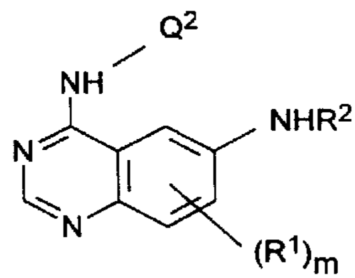
V

wherein each of L^1 and L^2, which may be the same or different, is a suitable ligand as defined hereinbefore, with a compound of the formula Q^1-Z wherein Z is a displaceable group as defined hereinbefore.

The reaction is conveniently carried out in a suitable inert solvent or diluent and at a suitable temperature in an analogous manner to the conditions described in paragraph (b) hereinbefore.

The quinazoline of the formula V may conveniently be obtained by analogous procedures to those described hereinbefore for the preparation of the organoboron reagent of the formula Q^1-$B(L^1)(L^2)$.

(d) For the production of those compounds of the formula I wherein X^1 is a group of the formula $N(R^2)CO$ or $N(R^2)SO_2$, the acylation of an amine of the formula VI



VI

with a carboxylic acid of the formula Q^1-CO_2H, or a reactive derivative thereof, or a sulphonic acid of the formula Q^1-SO_2OH, or a reactive derivative thereof, as appropriate.

A suitable reactive derivative of a carboxylic acid of the formula Q^1-CO_2H is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as methanol, ethanol, isopropanol, butanol or N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and azide such as

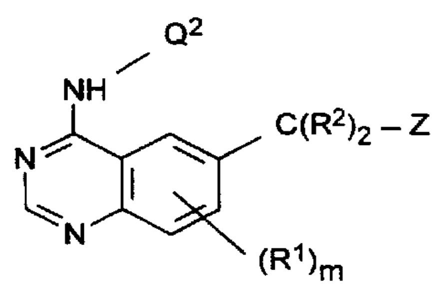
diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide. Analogously suitable reactive derivatives of the sulphonic acid of the formula Q^1-SO_2OH may be obtained.

The reaction is conveniently carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

(e) For the production of those compounds of the formula I wherein X^1 is a group of the formula $OC(R^2)_2$, $SC(R^2)_2$ or $N(R^2)C(R^2)_2$, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of an appropriate phenol, thiophenol or aniline with an alkylating agent of the formula Z-$C(R^2)_2$-Q^1 wherein Z is a displaceable group as defined hereinbefore.

The reaction is conveniently carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, preferably at or near 80°C.

(f) For the production of those compound of the formula I wherein X^1 is a group of the formula $C(R^2)_2O$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of the appropriate phenol of the formula HO-Q^1, thiophenol of the formula HS-Q^1 or aniline of the formula R^2NH-Q^1, with an alkylating agent of the formula VII



VII

wherein Z is a displaceable group as defined hereinbefore.

The reaction is conveniently carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0 to 150°C, preferably in the range 20 to 70°C.

(g) For the production of those compounds of the formula I which possess an aminomethyl substituent or wherein X^1 is a group of the formula $N(R^2)CH_2$ or $CH_2N(R^2)$, the

reduction of a compound of the formula I which possesses a cyano substituent or wherein X^1 is a group of the formula $N(R^2)CO$ or $CON(R^2)$ as appropriate.

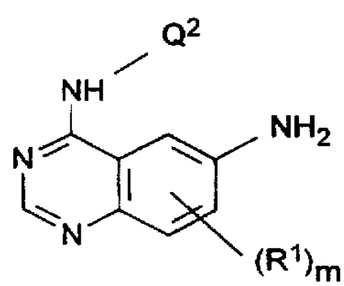
The reduction may be carried out by any of the many procedures known in the art for such transformations. A suitable reducing agent is, for example, an alkali metal aluminium hydride such as lithium aluminium hydride.

The reduction is conveniently carried out in a suitable inert solvent or diluent such as diethyl ether or tetrahydrofuran and at a temperature in the range, for example, 0 to 80°C, preferably in the range 15 to 50°C.

(h) For the production of those compounds of the formula I which possess an amino substituent, the reduction of a compound of the formula I which possesses a nitro substituent.

The reduction may conveniently be carried out by any of the many procedures known for such a transformation. The reduction may be carrried out, for example, by the hydrogenation of a solution of the nitro compound in an inert solvent or diluent as defined hereinbefore in the presence of a suitable metal catalyst such as palladium or platinum. A further suitable reducing agent is, for example, an activated metal such as activated iron (produced by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be carried out by heating a mixture of the nitro compound and the activated metal in a suitable solvent or diluent such as a mixture of water and an alcohol, for example. methanol or ethanol, to a temperature in the range, for example, 50 to 150°C, conveniently at or near 70°C.

(i) For the production of those compounds of the formula I wherein X^1 is a group of the formula $NHCH(R^2)$, the reductive amination of a keto compound of the formula R^2-CO-Q^1 with an amine of the formula VIII



VIII

Any reducing agent known in the art for promoting a reductive amination reaction may be employed. A suitable reducing agent is, for example, a hydride reducting agent, for

example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

(j) For the production of those compounds of the formula I wherein X^1 is a group of the formula O, S or $N(R^2)$, the coupling, conveniently in the presence of a suitable base as defined hereinbefore, of an appropriate phenol, thiophenol or aniline with a compound of the formula $Z\text{-}Q^1$ wherein Z is a displaceable group as defined hereinbefore.

Conveniently the reaction may be performed in the presence of a suitable catalyst, for example a metallic catalyst such as a palladium(0) or copper(I) catalyst, for example tetrakis(triphenylphosphine)palladium(0), cuprous chloride or cuprous bromide.

The coupling reaction is conveniently performed in a suitable inert solvent or diluent as defined hereinbefore, preferably in N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, 10 to 150°C, conveniently at or near 100°C.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required, for example a mono- or di-acid-addition salt, it may be obtained, for example, by reaction of said compound with, for example, a suitable acid using a conventional procedure.

As stated hereinbefore the quinazoline derivative defined in the present invention possesses anti-proliferative activity such as anti-cancer activity which is believed to arise from the Class I receptor tyrosine kinase inhibitory activity of the compound. These properties may be assessed, for example, using one or more of the procedures set out below:-

(a) An in vitro assay which determines the ability of a test compound to inhibit the enzyme EGF receptor tyrosine kinase. Receptor tyrosine kinase was obtained in partially purified form from A-431 cells (derived from human vulval carcinoma) by the procedures described below which are related to those described by Carpenter et al., J. Biol. Chem., 1979,

254, 4884, Cohen et al., J. Biol. Chem., 1982, 257, 1523 and by Braun et al., J. Biol. Chem., 1984, 259, 2051.

A-431 cells were grown to confluence using Dulbecco's modified Eagle's medium DMEM) containing 5% fetal calf serum (FCS). The obtained cells were homogenised in a hypotonic borate/EDTA buffer at pH 10.1. The homogenate was centrifuged at 400 g for 10 minutes at 0-4°C. The supernatant was centrifuged at 25,000 g for 30 minutes at 0-4°C. The pelleted material was suspended in 30 mM Hepes buffer at pH 7.4 containing 5% glycerol, 4 mM benzamidine and 1% Triton X-100, stirred for 1 hour at 0-4°C, and recentrifuged at 100,000 g for 1 hour at 0-4°C. The supernatant, containing solubilised receptor tyrosine kinase, was stored in liquid nitrogen.

For test purposes 40 μl of the enzyme solution so obtained was added to a mixture of 400 μl of a mixture of 150 mM Hepes buffer at pH 7.4, 500 μM sodium orthovanadate, 0.1% Triton X-100, 10% glycerol, 200 μl water, 80 μl of 25 mM DTT and 80 μl of a mixture of 12.5 mM manganese chloride, 125 mM magnesium chloride and distilled water. There was thus obtained the test enzyme solution.

Each test compound was dissolved in dimethylsulphoxide (DMSO) to give a 50 mM solution which was diluted with 40 mM Hepes buffer containing 0.1% Triton X-100, 10% glycerol and 10% DMSO to give a 500 μM solution. Equal volumes of this solution and a solution of epidermal growth factor (EGF; 20 μg/ml) were mixed.

[γ-^{32}P]ATP (3000 Ci/mM, 250 μCi) was diluted to a volume of 2 ml by the addition of a solution of ATP (100 μM) in distilled water. An equal volume of a 4 mg/ml solution of the peptide Arg-Arg-Leu-Ile-Glu-Asp-Ala-Glu-Tyr-Ala-Ala-Arg-Gly in a mixture of 40 mM Hepes buffer at pH 7.4, 0.1% Triton X-100 and 10% glycerol was added.

The test compound/EGF mixture solution (5 μl) was added to the test enzyme solution (10 μl) and the mixture was incubated at 0-4°C for 30 minutes. The ATP/peptide mixture (10 μl) was added and the mixture was incubated at 25°C for 10 minutes. The phosphorylation reaction was terminated by the addition of 5% trichloroacetic acid (40 μl) and bovine serum albumin (BSA; 1 mg/ml, 5 μl). The mixture was allowed to stand at 4°C for 30 minutes and then centrifuged. An aliquot (40 μl) of the supernatant was placed onto a strip of Whatman p 81 phosphocellulose paper. The strip was washed in 75 mM phosphoric acid (4 x 10 ml) and blotted dry. Radioactivity present in the filter paper was measured using a liquid scintillation counter (Sequence A). The reaction sequence was repeated in the

absence of the EGF (Sequence B) and again in the absence of the test compound (Sequence C).

Receptor tyrosine kinase inhibition was calculated as follows:-

$$\% \text{ Inhibition} = \frac{100 - (A-B)}{C - B} \times 100$$

The extent of inhibition was then determined at a range of concentrations of test compound to give an IC_{50} value.

(b) An in vitro assay which determines the ability of a test compound to inhibit the EGF-stimulated growth of the human naso-pharyngeal cancer cell line KB.

KB cells were seeded into wells at a density of 1×10^4 - 1.5×10^4 cells per well and grown for 24 hours in DMEM supplemented with 5% FCS (charcoal-stripped). Cell growth was determined after incubation for 3 days by the extent of metabolism of MTT tetrazolium dye to furnish a bluish colour. Cell growth was then determined in the presence of EGF (10 ng/ml) or in the presence of EGF (10 ng/ml) and a test compound at a range of concentrations. An IC_{50} value could then be calculated.

(c) An in vivo assay in a group of male rats which determines the ability of a test compound (usually administered orally as a ball-milled suspension in 0.5% polysorbate) to inhibit the stimulation of liver hepatocyte growth caused by the administration of the growth factor TGFα (400 μg/kg subcutaneously, usually dosed twice, 3 and 7 hours respectively after the administration of the test compound).

In a control group of rats, the administration of TGFα causes on average a 5-fold stimulation of liver hepatocyte growth.

Cell-growth in the control and test animals is determined as follows:-

On the morning of the day after the dosing of the test compound (or 0.5% polysorbate in the control group), the animals are dosed with bromodeoxyuridine (BrdU; 100 mg/kg intraperitoneally). The animals are killed four hours later and the livers are excised. Slices are cut from each liver and the uptake of BrdU is determined by a conventional immunohistochemical technique similar to that described on pages 267 and 268 of an article by Goldsworthy et al. in Chemically Induced Cell Proliferation: Implications for Risk Assessment, Wiley-Liss Inc., 1991, pages 253-284. Further tests were carried out using a range of doses of the test compounds to allow the calculation of an approximate ED_{50} value

for the inhibition of liver hepatocyte proliferation as determined by inhibition of the uptake of BrdU.

(d) An in-vivo assay in a group of athymic nude mice (strain ONU:Alpk) which determines the ability of a test compound (usually administered orally as a ball-milled suspension in 0.5% polysorbate) to inhibit the growth of xenografts of the human vulval epidermoid carcinoma cell line A-431.

A-431 cells were maintained in culture in DMEM supplemented with 5% FCS and 2mM glutamine. Freshly cultured cells were harvested by trypsinization and injected subcutaneously (10 million cells/0.1 ml/mouse) into both flanks of a number of donor nude mice. When sufficient tumour material was available (after approximately 9 to 14 days), fragments of tumour tissue were transplanted into the flanks of recipient nude mice (test day 0). Generally, on the seventh day after transplantation (test day 7) groups of 7 to 10 mice with similar-sized tumours were selected and dosing of the test compound was commenced. Once-daily dosing of test compound was continued for a total of 13 days (test days 7 to 19 inclusive). In some studies the dosing of the test compound was continued beyond test day 19, for example to test day 26. In each case, on the following day the animals were killed and final tumour volume was calculated from measurements of the length and width of the tumours. Results were calculated as a percentage inhibition of tumour volume relative to untreated controls.

Although the pharmacological properties of the compounds of the formula I vary with structural change as expected, in general activity possessed by compounds of the formula I may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.01-1 μM;

Test (b):- IC_{50} in the range, for example, 0.1-10 μM;

Test (c):- ED_{50} in the range, for example, 1-100 mg/kg;

Test (d):- 20 to 70% inhibition of tumour volume from a daily dose in the range, for example, 50 to 400 mg/kg.

Thus, by way of example, the compound 4-(3-chloro-4-fluoroanilino)-6-[5-(2-morpholinoethyl)thien-2-yl]quinazoline has an IC_{50} of 0.04 μM in Test (a), an IC_{50} of 0.19 μM in Test (b) and gives 64% inhibition in Test (d) at a dosage of 50 mg/kg/day.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The quinazoline derivative will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-100 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a quinazoline derivative of the formula I as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have now found that the compounds of the present invention possess anti-proliferative properties which are believed to arise from their Class I (EGF type) receptor tyrosine kinase inhibitory activity. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by Class I receptor tyrosine kinase enzymes, i.e. the compounds may be used to produce a Class I receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of Class I receptor tyrosine kinase enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of Class I receptor tyrosine kinase. Accordingly the compounds of the present invention are expected to be useful in the treatment of cancer by

providing an anti-proliferative effect, particularly in the treatment of Class I receptor tyrosine kinase sensitive cancers such as cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas and ovary. The compounds of the present invention are also expected to be useful in the treatment of other cell-proliferation diseases such as psoriasis, benign prostatic hypertrophy, atherosclerosis and restenosis.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative as defined immediately above.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional radiotherapy or one or more other anti-tumour substances, for example cytotoxic or cytostatic anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine, vindesine and vinorelbine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, tegafur, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 239362 such as N-{5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl}-L-glutamic acid; intercalating antibiotics, for example adriamycin, mitomycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide and camptothecin; biological response modifiers, for example interferon; and anti-hormones, for example antioestrogens such as tamoxifen, for example antiandrogens such as 4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide or, for example LHRH antagonists or LHRH agonists such as

goserelin, leuprorelin or buserelin and hormone synthesis inhibitors, for example aromatase inhibitors such as those disclosed in European Patent Application No. 0296749, for example 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropionitrile), and, for example, inhibitors of 5α-reductase such as 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

As stated above the quinazoline derivative defined in the present invention is an effective anti-cancer agent, which property is believed to arise from its Class I (EGF type) receptor tyrosine kinase inhibitory properties. Such a quinazoline derivative of the invention is expected to possess a wide range of anti-cancer properties as Class I receptor tyrosine kinases have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a quinazoline derivative of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a quinazoline derivative of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas.

It is further expected that a quinazoline derivative of the present invention will possess activity against other cell-proliferation diseases such as psoriasis, benign prostatic hypertrophy, atherosclerosis and restenosis.

It is also to be expected that a quinazoline derivative of the invention will be useful in the treatment of additional disorders of cellular growth in which aberrant cell signalling by way of receptor tyrosine kinase enzymes, including as yet unidentified receptor tyrosine kinase enzymes, are involved. Such disorders include, for example, inflammation, angiogenesis, vascular restenosis, immunological disorders, pancreatitis, kidney disease and blastocyte maturation and implantation.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multilicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet, unless otherwise stated end-products of the formula I were dissolved in CD_3SOCD_3 for the determination of NMR values.

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), infra-red (IR) or NMR analysis;

(viii) the following abbreviations have been used:-

DMF N,N-dimethylformamide;

DMA N,N-dimethylacetamide;

NMP N-methylpyrrolidin-2-one;

THF tetrahydrofuran;

DME 1,2-dimethoxyethane.

Example 1

Tetrakis(triphenylphosphine)palladium(0) (0.04 g) was added to a stirred mixture of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt (0.25 g), a saturated aqueous sodium bicarbonate solution (1.5 ml), di-isopropyl 4-cyanophenylboronate and DME (10 ml). The resultant mixture was stirred and heated to reflux for 3 hours. The mixture was cooled to ambient temperature. An aqueous sodium hydroxide solution (5M, 2 ml) and water were added in turn and the resultant precipitate was isolated by filtration, dried and purified by column chromatography using a 10:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(4-cyanophenyl)quinazoline (0.05 g, 18%), m.p. >250°C;

NMR Spectrum: 7.5 (t, 1H), 7.85 (m, 1H), 7.9 (d, 1H), 8.0-8.15 (m, 4H), 8.2 (m, 1H), 8.55 (m, 1H), 8.65 (s, 1H), 8.9 (d, 1H), 10.0 (broad s, 1H);

Elemental Analysis: Found C, 66.1; H, 3.3; N, 14.3;

$C_{21}H_{12}ClFN_4$ $0.35H_2O$ requires C, 66.2; H, 3.4; N, 14.7%.

The 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt used as a starting material was obtained as follows:-

A mixture of 5-bromoanthranilic acid (15.2 g) and formamide (20 ml) was heated to 140°C for 2 hours and then to 190°C for 2 hours. The mixture was cooled to ambient temperature. Methanol (20 ml) was added and the mixture was heated to reflux for 5 minutes. Water (150 ml) was added and the mixture was cooled to ambient temperature. The precipitate was washed with water and dried. There was thus obtained 6-bromo-3,4-dihydroquinazolin-4-one (14.1 g).

A mixture of a portion (2.85 g) of the material so obtained, thionyl chloride (30 ml) and DMF (4 drops) was stirred and heated to reflux for 3 hours. The mixture was evaporated to give 6-bromo-4-chloroquinazoline which was used without further purification.

A mixture of the material so obtained, 3-chloro-4-fluoroaniline (1.85 g) and isopropanol (30 ml) was stirred and heated to reflux for 3 hours. The mixture was allowed to cool to ambient temperature and the solid was isolated, washed in turn with isopropanol and diethyl ether and dried. There was thus obtained 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt, (2.65 g);

NMR Spectrum: 7.53 (t, 1H), 7.8 (m, 1H), 7.94 (d, 1H), 8.09 (m, 1H), 8.26 (m, 1H), 8.98 (s, 1H), 9.3 (d, 1H);

Elemental Analysis: Found C, 43.2; H, 2.4; N, 10.6;

$C_{14}H_8BrClFN_3$ 1HCl requires C, 43.2; H, 2.3; N, 10.8%.

The di-isopropyl 4-cyanophenylboronate used as a starting material was obtained as follows:-

n-Butyllithium (1.6M in hexane, 1 ml) was added dropwise to a stirred mixture of 4-bromobenzonitrile (0.254 g), tri-isopropyl borate (0.4 ml) and THF (10 ml) which had been colled to -78°C. The resultant mixture was stirred and allowed to warm to ambient temperature. The mixture was evaporated to give the required starting material which was used without further purification.

Example 2

Tetrakis(triphenylphosphine)palladium(0) (0.019 g) and a solution of phenylboronic acid (0.083 g) in ethanol (1 ml) were added in turn to a stirred mixture of 6-bromo-4-(3-methylanilino)quinazoline hydrochloride salt (European Patent Application No. 0520722, Example 9 thereof, 0.245 g), a saturated aqueous sodium carbonate solution (0.4 ml) and toluene (1.2 ml). The resultant mixture was stirred and heated to reflux for 6 hours. The mixture was cooled to ambient temperature and partitioned between methylene chloride and water. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using a 4:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-(3-methylanilino)-6-phenylquinazoline (0.159 g), m.p. 207-209°C;

NMR Spectrum: 2.3 (s, 3H), 6.95 (d, 1H), 7.3 (t, 1H), 7.4-7.9 (m, 8H), 8.2 (m, 1H), 8.6 (s, 1H), 8.85 (m, 1H), 9.8 (broad s, 1H);

Elemental Analysis: Found C, 78.8; H, 5.5; N, 12.7;

$C_{21}H_{17}N_3$ $0.5H_2O$ requires C, 78.7; H, 5.6; N, 13.1%.

Example 3

Lithium aluminium hydride (1M in diethyl ether, 20 ml) was added dropwise to a stirred mixture of 4-(3-chloro-4-fluoroanilino)-6-(4-cyanophenyl)quinazoline (0.706 g), diethyl ether (25 ml) and THF (25 ml) and the resultant mixture was stirred at ambient

temperature for 16 hours. The mixture was cooled to 0°C. Water (2 ml), 5M aqueous sodium hydroxide solution (2 ml) and water (6 ml) were added in turn and the mixture was allowed to warm to ambient temperature. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using a 10:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 6-(4-aminomethylphenyl)-4-(3-chloro-4-fluoroanilino)quinazoline (0.409 g);

NMR Spectrum: 4.0 (s, 2H), 7.4 (t, 1H), 7.6 (d, 2H), 7.8-8.0 (m, 4H), 8.2 (m, 2H), 8.6 (s, 1H), 8.9 (s, 1H), 10.1 (broad s, 1H).

Example 4

Tetrakis(triphenylphosphine)palladium(0) (0.05 g) and a saturated aqueous sodium bicarbonate solution (5 ml) were added in turn to a stirred mixture of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt (0.35 g), 3-furylboronic acid (J. Het. Chem., 1975, 195; 0.208 g) and DME (15 ml). The resultant mixture was stirred and heated to reflux for 2 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using initially methylene chloride and then increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(3-furyl)quinazoline;

NMR Spectrum: 7.16 (m, 1H), 7.48 (t, 1H), 7.82 (d, 1H), 7.85 (m, 2H), 8.16 (m, 1H), 8.18 (m, 1H), 8.35 (d, 1H), 8.61 (s, 1H), 8.7 (d, 1H), 9.88 (s, 1H);

Elemental Analysis: Found C, 62.8; H, 3.4; N, 10.8;

$C_{18}H_{11}ClFN_3O$ $0.25H_2O$ requires C, 62.8; H, 3.3; N, 12.2%.

Example 5

Tetrakis(triphenylphosphine)palladium(0) (0.05 g) was added to a stirred mixture of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt (0.613 g), a saturated aqueous sodium bicarbonate solution (10 ml), di-isopropyl 2-furylboronate and DME (20 ml). The resultant mixture was stirred and heated to reflux for 1.5 hours. The mixture was cooled to ambient temperature. An aqueous sodium hydroxide solution (5M, 10 ml) and water were added in turn. The resultant precipitate was isolated, washed with a small amount of

methylene chloride and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(2-furyl)quinazoline (0.54 g), m.p. 232-234°C;

NMR Spectrum: 6.7 (m, 1H), 7.15 (d, 1H), 7.4 (t, 1H), 7.8 (m, 3H), 8.2 (m, 2H), 8.55 (s, 1H), 8.8 (d, 1H), 10.0 (broad s, 1H);

Elemental Analysis: Found C, 57.8; H, 3.6; N, 10.9;

$C_{18}H_{11}ClFN_3O$ $1.9H_2O$ requires C, 57.8; H, 4.0; N, 11.2%.

The di-isopropyl 2-furylboronate used as a starting material was obtained as follows:-

n-Butyllithium (1.6M in hexane, 2.75 ml) was added dropwise to a stirred solution of furan (0.25 g) in THF (10 ml) which had been cooled to 0°C. The resultant mixture was stirred at ambient temperature for 20 minutes. The mixture was cooled to -78°C and tri-isopropyl borate (1 ml) was added dropwise. The mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The mixture was evaporated to give the required starting material which was used without further purification.

Example 6

Using an analogous procedure to that described in Example 5 except that the reaction mixture was heated to reflux for 3 hours, 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt was reacted with di-isopropyl 2-thienylboronate to give 4-(3-chloro-4-fluoroanilino)-6-(2-thienyl)quinazoline in 36% yield, m.p. 205-208°C;

NMR Spectrum: 7.2 (m, 1H), 7.4 (t, 1H), 7.7 (m, 2H), 7.8 (m, 2H), 8.15 (m, 2H), 8.55 (s, 1H), 8.75 (d, 1H), 10.0 (broad s, 1H);

Elemental Analysis: Found C, 58.6; H, 3.1; N, 11.3;

$C_{18}H_{11}ClFN_3S$ $0.75H_2O$ requires C, 58.5; H, 3.4; N, 11.4%.

The di-isopropyl 2-thienylboronate used as a starting material was obtained as follows:-

n-Butyllithium (1.6M in hexane, 2 ml) was added dropwise to a stirred solution of 2-bromothiophene (0.515 g) in THF (6 ml) which had been cooled to -78°C. Tri-isopropyl borate (0.75 ml) was added dropwise and the resultant mixture was stirred and allowed to warm to ambient temperature. The mixture was evaporated to give the required starting material which was used without further purification.

Example 7

Using an analogous procedure to that described in Example 5 except that the reaction mixture was heated to reflux for 2 hours, 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt was reacted with di-isopropyl 3-thienylboronate to give 4-(3-chloro-4-fluoroanilino)-6-(3-thienyl)quinazoline in 51% yield, m.p. 195-197°C;
NMR Spectrum: 7.5 (t, 1H), 7.7-7.9 (m, 4H), 8.05 (m, 1H), 8.2 (m, 1H), 8.25 (m, 1H), 8.6 (s, 1H), 8.8 (d, 1H), 9.9 (broad s, 1H);
Elemental Analysis: Found C, 57.8; H, 3.3; N, 10.6;
$C_{18}H_{11}ClFN_3S$ $1.15H_2O$ requires C, 57.4; H, 3.6; N, 11.2%.

The di-isopropyl 3-thienylboronate used as a starting material was obtained by the reaction of 3-bromothiophene and tri-isopropyl borate using an analogous procedure to that described in the portion of Example 6 which is concerned with the preparation of starting materials.

Example 8

Using an analogous procedure to that described in Example 5 except that the reaction mixture was heated to reflux for 4 hours, 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt was reacted with di-isopropyl 5-(2-morpholinoethyl)thien-2-ylboronate. The reaction mixture was cooled to ambient temperature and partitioned between methylene chloride and water. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of hexane and ethyl acetate to give 4-(3-chloro-4-fluoroanilino)-6-[5-(2-morpholinoethyl)thien-2-yl]quinazoline in 27% yield;
NMR Spectrum: 2.6-2.7 (t, 2H), 3.0 (t, 2H), 3.65 (t, 4H), 7.0 (d, 1H), 7.45 (t, 1H), 7.55 (d, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.2 (m, 1H), 8.6 (s, 1H), 8.75 (d, 1H), 9.95 (broad s, 1H);
Elemental Analysis: Found C, 59.0; H, 4.9; N, 11.3;
$C_{24}H_{22}ClFN_4OS$ $1H_2O$ requires C, 59.2; H, 5.0; N, 11.5%.

The di-isopropyl 5-(2-morpholinoethyl)thien-2-ylboronate used as a starting material was obtained as follows:-

2-(2-Thienyl)acetyl chloride (16 g) was added slowly to a stirred mixture of morpholine (17.5 ml) and methylene chloride (150 ml). A further portion (5 ml) of morpholine was added and the mixture was stirred at ambient temperature for 4 hours. The

reaction mixture was washed in turn with 2M aqueous hydrochloric acid, a saturated aqueous sodium bicarbonate solution and brine. The organic phase was dried and evaporated. The residue was triturated under a mixture of hexane and diethyl ether to give N-[2-(2-thienyl)acetyl]morpholine (20.9 g).

Lithium aluminium hydride (1M in diethyl ether, 28.3 ml) was added slowly to a stirred solution of N-[2-(2-thienyl)acetyl]morpholine (3 g) in THF (100 ml). The resultant mixture was heated to 45°C for 30 minutes. A 2M aqueous hydrochloric acid solution was added dropwise to destroy the excess of reducing agent and the mixture was partitioned between methylene chloride and a 2M aqueous sodium hydroxide solution. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to give 2-(2-morpholinoethyl)-thiophene (1.7 g).

A portion (1.22 g) of the material so obtained was dissolved in THF (75 ml) and the solution was cooled to -78°C. n-Butyllithium (1.6M in hexane, 3.86 ml) was added dropwise and the mixture was stirred at -78°C for 30 minutes. A solution of tri-isopropyl borate (1.16 ml) in THF (25 ml) was added and the reaction mixture was then allowed to warm to ambient temperature. The mixture was evaporated to give di-isopropyl 5-(2-morpholinoethyl)thien-2-ylboronate which was used without further purification.

Example 9

Using an analogous procedure to that described in Example 5 except that the reaction mixture was heated to reflux for 2 hours, 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt was reacted with di-isopropyl 5-morpholinomethylthien-3-ylboronate. The reaction mixture was cooled to ambient temperature and partitioned between methylene chloride and water. The organic phase was washed with brine, dried and evaporated. The residue was purified by column chromatography using a 25:1 mixture of methylene chloride and methanol as eluent. The resultant product was recrystallised from ethyl acetate. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(5-morpholinomethylthien-3-yl)quinazoline in 30% yield;

NMR Spectrum: 2.5 (t, 4H), 3.6 (t, 4H), 3.75 (s, 2H), 7.45 (t, 1H), 7.6 (d, 1H), 7.8 (m, 2H), 7.95 (d, 1H), 8.22 (m, 2H), 8.6 (s, 1H), 8.75 (d, 1H), 9.9 (broad s, 1H);

Elemental Analysis: Found C, 58.5; H, 4.8; N, 11.7;

$C_{23}H_{20}ClFN_4OS$ $1H_2O$ requires C, 58.4; H, 4.7; N, 11.8%.

The di-isopropyl 5-morpholinomethylthien-3-ylboronate used as a starting material was obtained as follows:-

Sodium cyanoborohydride (2 g) was added portionwise to a stirred mixture of 4-bromo-2-thiophenecarbaldehyde (4.78 g), morpholine (2.1 g), glacial acetic acid (1.8 g) and ethanol (125 ml). The mixture was stirred at ambient temperature for 1 hour. The mixture was poured into a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride. The organic phase was washed with brine and evaporated. The resultant oil was partitioned between a dilute (10%) aqueous hydrochloric acid solution and methylene chloride. The aqueous phase was basified by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated to give 4-bromo-2-morpholinomethylthiophene (3.2 g);
<u>NMR Spectrum</u>: 2.4 (t, 4H), 3.55 (t, 4H), 3.65 (s, 2H), 6.95 (d, 1H), 7.5 (d, 1H).

A portion (1.22 g) of the material so obtained was dissolved in THF (100 ml) and the solution was cooled to -78°C. Tri-isopropyl borate (0.963 g) and n-butyllithium (1.6M in hexane, 2.91 ml) were added in turn. The mixture was stirred at -78°C for 30 minutes and then allowed to warm to ambient temperature. The mixture was evaporated to give di-isopropyl 5-morpholinomethylthien-3-ylboronate which was used without further purification.

<u>Example 10</u>

A mixture of 6-(2-chloroacetyl)-4-(3-chloro-4-fluoroanilino)quinazoline (0.5 g) and formamide (2 ml) was stirred and heated to 140°C for 2 hours. The mixture was cooled to ambient temperature and water was added. The precipitate was isolated and purified by column chromatography on a C18 reversed-phase silica column using decreasingly polar mixtures of water and methanol (containing 0.2% of trifluoroacetic acid) as eluent. There were thus obtained in turn:-

4-(3-chloro-4-fluoroanilino)-6-(4-imidazolyl)quinazoline (0.135 g);
<u>NMR Spectrum</u>: 7.54 (t, 1H), 7.78 (m, 1H), 7.94 (d, 1H), 8.07 (d, 1H), 8.12 (m, 1H), 8.38 (m, 1H), 8.81 (s, 1H), 8.82 (s, 1H), 9.01 (s, 1H);
<u>Elemental Analysis</u>: Found C, 42.9; H, 2.5; N, 11.4;
$C_{17}H_{11}ClFN_5$ $1.4H_2O$ $2CF_3CO_2H$ requires C, 42.5; H, 2.7; N, 11.8%; and
4-(3-chloro-4-fluoroanilino)-6-(4-oxazolyl)quinazoline (0.056 g);
<u>NMR Spectrum</u>: 7.53 (t, 1H), 7.8 (m, 1H), 7.93 (d, 1H), 8.12 (m, 1H), 8.42 (m, 1H), 8.65

(s, 1H), 8.8 (s, 1H), 8.88 (s, 1H), 9.1 (d, 1H);

Elemental Analysis: Found C, 47.0; H, 2.3; N, 11.2;

$C_{17}H_{11}ClFN_4O$ 1.5CF_3CO_2H requires C, 46.9; H, 2.3; N, 10.9%.

The 6-(2-chloroacetyl)-4-(3-chloro-4-fluoroanilino)quinazoline used as a starting material was obtained as follows:-

Triphenylphosphine (0.063 g) was added to a stirred mixture of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline hydrochloride salt (2.34 g), triethylamine (3.4 ml), (trimethylsilyl)acetylene (1.33 ml) palladium(II) chloride (0.021 g), cuprous iodide (0.045 g) and DMF (15 ml). The mixture was stirred and heated to 90°C for 2 hours. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(2-trimethylsilylethynyl)quinazoline (2.2 g).

A mixture of a portion (2 g) of the material so obtained, potassium carbonate (0.25 g) and methanol (100 ml) was stirred at ambient temperature for 2 hours. The mixture was acidified to pH5 by the addition of glacial acetic acid. The resultant mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was dried ($MgSO_4$) and evaporated. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-ethynylquinazoline (1.68 g), m.p. 224-226°C;

NMR Spectrum: 4.42 (s, 1H), 7.45 (t, 1H), 7.59 (d, 1H), 7.8-7.93 (m, 2H), 8.23 (m, 1H), 8.65 (s, 1H), 8.77 (s, 1H), 9.8 (broad s, 1H).

A mixture of a portion (1.2 g) of the material so obtained, mercuric trifluoroacetate (0.1 g), water (1 ml) and trifluoroacetic acid (15 ml) was stirred and heated to reflux for 4 hours. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under methylene chloride. There was thus obtained 6-acetyl-4-(3-chloro-4-fluoroanilino)quinazoline (0.37 g), m.p. 211-213°C;

NMR Spectrum: 2.75 (s, 3H), 7.47 (t, 1H), 7.83 (m, 1H), 7.88 (d, 1H), 8.14 (m, 1H), 8.33 (m, 1H), 8.69 (s, 1H), 9.19 (d, 1H).

Chlorine gas was led into a stirred mixture of 6-acetyl-4-(3-chloro-4-fluoroanilino)-quinazoline (0.11 g), methylene chloride (40 ml) and ethanol (60 ml) and the mixture was cooled to a temperature in the range 20 to 25°C. After 10 minutes the supply of chlorine was stopped and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture

was evaporated to give 6-(2-chloroacetyl)-4-(3-chloro-4-fluoroanilino)quinazoline (0.114 g) which was used without further purification.

Example 11

A mixture of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline (0.5 g), 2-pyridyl-tri-n-butyltin (J. Het. Chem., 1990, 2165; 0.8 g), tetrakis(triphenylphosphine)palladium(0) (0.05 g) and THF (20 ml) was stirred and heated to 60°C for 4 days. The mixture was evaporated and the residue was purified by column chromatography using initially methylene chloride and then increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(2-pyridyl)quinazoline (0.11 g);
NMR Spectrum: 7.45 (m, 1H), 7.47 (t, 1H), 7.88 (m, 1H), 7.9 (d, 1H), 8.03 (m, 1H), 8.18 (d, 1H), 8.22 (d, 1H), 8.63 (m, 1H), 8.66 (s, 1H), 8.75 (m, 1H), 9.19 (d, 1H);
Elemental Analysis: Found C, 61.5; H, 3.6; N, 14.9;
$C_{19}H_{12}ClFN_4$ $1.1H_2O$ requires C, 61.6; H, 3.8; N, 15.1%.

Example 12

Diethyl-3-pyridylborane (0.176 g) was added to a mixture of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline (0.53 g), powdered potassium hydroxide (0.202 g), tetra-n-butylammonium bromide (0.042 g), tetrakis(triphenylphosphine)palladium(0) (0.069 g) and THF (10 ml). The resultant mixture was stirred and heated to reflux for 16 hours. The mixture was evaporated and the residue was purified by column chromatography using initially methylene chloride and then increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(3-pyridyl)quinazoline (0.125 g);
NMR Spectrum: 7.5 (t, 1H), 7.6 (m, 1H), 7.88 (m, 1H), 7.93 (d, 1H), 8.2 (m, 1H), 8.28 (m, 1H), 8.3 (m, 1H), 8.68 (m, 2H), 8.91 (d, 1H), 9.16 (d, 1H), 10.02 (broad s, 1H);
Elemental Analysis: Found C, 64.3; H, 3.3; N, 15.6;
$C_{19}H_{12}ClFN_4$ $0.25H_2O$ requires C, 64.2; H, 3.5; N, 15.8%.

Example 13

A mixture of 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline (0.576 g), 4-chloroquinazoline hydrochloride salt (0.83 g) and isopropanol (10 ml) was stirred and heated to reflux for 5 hours. The hot reaction mixture was filtered and the filtrate was allowed to cool to ambient temperature. The resultant solid was isolated, washed with isopropanol and with diethyl ether and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(4-quinazoline dihydrochloride salt (0.86 g);

NMR Spectrum: 7.54 (t, 1H), 7.8 (m, 1H), 7.92 (t, 1H), 8.0-8.2 (m, 4H), 8.38 (m, 1H), 8.97 (s, 1H), 8.98 (s, 1H), 9.06 (d, 1H), 9.28 (d, 1H), 11.75 (broad s, 1H), 12.26 (broad s, 1H);

Elemental Analysis: Found C, 53.4; H, 3.4; N, 16.9;

$C_{22}H_{14}ClFN_6$ 2HCl $0.33H_2O$ requires C, 53.2; H, 3.4; N, 16.9%.

The 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline used as a starting material was obtained as follows:-

3-Chloro-4-fluoroaniline (3.6 g) was added to a stirred mixture of 4-chloro-6-nitroquinazoline (European Patent Application No. 0566226, Example 8 thereof; 5 g); THF (10 ml) and DMF (10 ml). The resultant mixture was stirred at ambient temperature for 5 hours. The precipitate was isolated and partitioned between water and a 9:1 mixture of methylene chloride and methanol. The aqueous phase was neutralised by the addition of a saturated aqueous sodium bicarbonate solution and re-extracted with methylene chloride. The organic phases were combined and evaporated. The residue was triturated under a 9:1 mixture of ethanol and water. The resultant solid was isolated and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-nitroquinazoline (2.5 g).

A mixture of a portion (2.3 g) of the material so obtained, 10% palladium-on-carbon catalyst (0.4 g), ethanol (25 ml) and DMF (25 ml) was stirred under an atmosphere of hydrogen for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated under a 4:1 mixture of ethanol and water. The resultant solid was isolated and dried. There was thus obtained 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline (0.35 g, 17%);

NMR Spectrum: 5.6 (broad s, 2H), 7.27 (m, 1H), 7.32 (s, 1H), 7.41 (t, 1H), 7.55 (d, 1H), 7.8 (m, 1H), 8.19 (m, 1H), 8.38 (s, 1H), 9.53 (broad s, 1H);

Elemental Analysis: Found C, 58.1; H, 3.6; N, 19.0;

$C_{14}H_{10}ClFN_4$ requires C, 58.2; H, 3.5; N, 19.4%.

Example 14

A mixture of 6-amino-4-(3-methylanilino)quinazoline (European Patent Application No. 0566226, Example 8 thereof; 0.2 g), 2-fluoroimidazole 4-toluenesulphonic acid salt (0.2 g), 4-toluenesulphonic acid (0.26 g) and DMF (1 ml) was stirred and heated to 100°C for 16 hours. The mixture was cooled to ambient temperature and partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 6-(2-imidazolylamino)-4-(3-methylanilino)quinazoline (0.09 g), m.p. 256-258°C;

NMR Spectrum: 2.33 (s, 3H), 6.77 (d, 2H), 6.95 (d, 1H), 7.24 (t, 1H), 7.6 (m, 3H), 7.85 (m, 1H), 8.11 (m, 1H), 8.39 (s, 1H), 8.94 (s, 1H), 9.4 (s, 1H), 11.0 (s, 1H);

Elemental Analysis: Found C, 68.1; H, 5.3; N, 26.4;

$C_{18}H_{16}N_6$ requires C, 68.3; H, 5.1; N, 26.6%.

The 2-fluoroimidazole 4-toluenesulphonic acid salt used as a starting material was obtained from 2-aminoimidazole using analogous procedures to those described in J. Het. Chem., 1978, 1227 and J. Amer. Chem. Soc., 1973, 4619.

Example 15

1-Methylimidazole-4-sulphonyl chloride (0.181 g) was added to a stirred mixture of 6-amino-4-(3-methylanilino)quinazoline (0.25 g) and pyridine (10 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residual oily solid was washed with methylene chloride and with a saturated aqueous sodium bicarbonate solution. The solid was then washed with water and with acetone and dried. There was thus obtained 4-(3-methylanilino)-6-(1-methylimidazole-4-sulphonamido)quinazoline (0.07 g), m.p. >250°C;

NMR Spectrum: (CD_3SOCD_3 + CD_3CO_2D) 2.37 (s, 3H), 3.64 (s, 3H), 6.98 (d, 1H), 7.27 (t, 1H), 7.5-7.8 (m, 6H), 8.2 (d, 1H), 8.48 (s, 1H);

Elemental Analysis: Found C, 54.7; H, 4.4; N, 19.7;

$C_{19}H_{18}N_6O_2S$ 1.2H_2O requires C, 54.8; H, 4.9; N, 20.2%.

Example 16

Sodium cyanoborohydride (0.126 g) was added portionwise to a stirred mixture of 6-amino-4-(3-methylanilino)quinazoline (0.25 g), 3-thiophenecarbaldehyde (0.26 ml), glacial acetic acid (0.114 ml) and ethanol (20 ml). The resultant mixture was stirred at ambient temperature for 16 hours. The mixture was basified by the addition of a saturated aqueous sodium bicarbonate solution and evaporated. The residue was washed with water and dried. There was thus obtained 4-(3-methylanilino)-6-(3-thienylmethylamino)quinazoline (0.335 g), m.p. 207-208°C;

NMR Spectrum: 2.3 (s, 3H), 4.45 (d, 2H), 6.52 (d, 1H), 6.9 (t, 1H), 7.2 (m, 1H), 7.3 (m, 3H), 7.5 (m, 3H), 7.65 (m, 2H), 8.3 (s, 1H), 9.2 (broad s, 1H);

Elemental Analysis: Found C, 68.6; H, 5.2; N, 15.3;

$C_{20}H_{18}N_4S$ $0.3H_2O$ requires C, 68.3; H, 5.3; N, 15.9%.

Example 17

Sodium cyanoborohydride (0.126 g) was added portionwise to a stirred mixture of 6-amino-4-(3-methylanilino)quinazoline (0.25 g), 2-imidazolecarbaldehyde (0.192 g), glacial acetic acid (0.114 ml) and ethanol (20 ml). The resultant mixture was stirred at ambient temperature for 3 hours. The mixture was basified by the addition of a saturated aqueous sodium bicarbonate solution and evaporated. The residue was washed with water and dried. There was thus obtained 6-(2-imidazolylmethylamino)-4-(3-methylanilino)quinazoline (0.096 g), m.p. 235-237°C;

NMR Spectrum: (CD_3SOCD_3 + CD_3CO_2D, 100°C) 2.3 (s, 3H), 4.45 (d, 2H), 6.5 (t, 1H), 6.9 (d, 1H), 7.1 (s, 2H), 7.3 (m, 3H), 7.5 (d, 1H), 7.65 (m, 2H), 8.3 (s, 1H), 9.2 (s, 1H), 12.0 (s, 1H);

Elemental Analysis: Found C, 67.4; H, 5.3; N, 24.8;

$C_{19}H_{18}N_6$ $0.5H_2O$ requires C, 67.3; H, 5.6; N, 24.8%.

Example 18

2-Thiophenecarbonyl chloride (0.6 g) was added portionwise to a stirred solution of 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline (1.04 g) in DMA (10 ml). The mixture was stirred at ambient temperature for 30 minutes. Methylene chloride (25 ml) was added and the

precipitate was isolated and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(thiophene-2-carboxamido)quinazoline hydrochloride salt (1.35 g), m.p. >250°C;
NMR Spectrum: 7.27 (m, 1H), 7.54 (t, 1H), 7.7 (m, 1H), 7.9 (m, 1H), 8.0 (m, 2H), 8.28 (m, 2H), 8.9 (s, 1H), 9.2 (d, 1H), 10.99 (s, 1H), 11.5 (broad s, 1H);
Elemental Analysis: Found C, 52.1; H, 3.3; N, 12.9;
$C_{19}H_{12}ClFN_4OS$ 1HCl 0.15DMA requires C, 52.5; H, 3.2; N, 13.0%.

Example 19

Lithium aluminium hydride (1M in diethyl ether, 7.1 ml) was added dropwise to a stirred mixture of 4-(3-chloro-4-fluoroanilino)-6-(thiophene-2-carboxamido)quinazoline hydrochloride salt (1 g) and THF (200 ml). The mixture was stirred at ambient temperature for 2 hours and then heated to 45°C for 1 hour. The mixture was cooled to ambient temperature and glacial acetic acid (5 ml) was added to destroy the excess of reducing agent. The mixture was evaporated and the residue was partitioned between methylene chloride and a 5M aqueous sodium hydroxide solution. The organic phase was washed with brine, dried and evaporated. The residue was purified by column chromatography using a 99:1 mixture of methylene chloride and methanol as eluent. The product so obtained as triturated under diethyl ether. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(2-thienylmethylamino)quinazoline (0.095 g), m.p. 193-195°C;
NMR Spectrum: 4.65 (d, 2H), 6.75 (t, 1H), 7.0 (m, 1H), 7.4 (m, 4H), 7.55 (d, 1H), 7.8 (m, 1H), 8.15 (m, 1H), 8.4 (s, 1H), 9.4 (broad s, 1H);
Elemental Analysis: Found C, 59.3; H, 3.8; N, 14.0;
$C_{19}H_{14}ClFN_4S$ $0.1Et_2O$ requires C, 59.4; H, 3.85; N, 14.3%.

Example 20

2-Furoyl chloride (0.287 g) was added portionwise to a stirred solution of 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline (0.577 g) in DMA (3 ml) and the resultant mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(furan-2-carboxamido)quinazoline (0.436 g);
NMR Spectrum: 6.75 (m, 1H), 7.56 (m, 2H), 7.69 (m, 1H), 8.0 (m, 3H), 8.27 (m, 1H), 8.91

(s, 1H), 9.13 (d, 1H), 10.85 (broad s, 1H), 11.5 (broad s, 1H);

Elemental Analysis: Found C, 54.3; H, 3.1; N, 13.3;

$C_{19}H_{12}ClFN_4O_2$ requires C, 54.3; H, 3.1; N, 13.4%.

Example 21

Using an analogous procedure to that described in Example 19, 4-(3-chloro-4-fluoroanilino)-6-(furan-2-carboxamido)quinazoline was reduced to give 4-(3-chloro-4-fluoroanilino)-6-(2-furfurylamino)quinazoline in 16% yield, m.p. 197-199°C;

NMR Spectrum: 4.45 (d, 2H); 6.4 (m, 1H), 6.7 (m, 1H), 7.3-7.6 (m, 5H), 7.8 (m, 1H), 8.15 (m, 1H), 8.4 (s, 1H), 9.5 (m, 1H);

Elemental Analysis: Found C, 59.8; H, 3.7; N, 14.5;

$C_{19}H_{14}ClFN_4O$ $0.2CH_2Cl_2$ requires C, 59.8; H, 3.8; N, 14.5%.

Example 22

Using an analogous procedure to that described in Example 18, 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline was reacted with 5-isoxazolecarbonyl chloride to give 4-(3-chloro-4-fluoroanilino)-6-(isoxazole-5-carboxamido)quinazoline hydrochloride salt in 87% yield, m.p. >250°C;

NMR Spectrum: 7.4 (d, 1H), 7.5 (t, 1H), 7.65 (m, 2H), 8.0 (m, 2H), 8.85 (d, 1H), 8.9 (s, 1H), 11.4 (s, 1H);

Elemental Analysis: Found C, 50.8; H, 3.3; N, 16.3;

$C_{18}H_{11}ClFN_5O_2$ 1HCl $0.4H_2O$ 0.24DMA requires C, 50.8; H, 3.4; N, 16.4%.

Example 23

N,N'-Dicyclohexylcarbodiimide (0.416 g) was added portionwise to a stirred mixture of 1,2,3-triazole-4-carboxylic acid (0.226 g) and DMA (10 ml). The resultant mixture was stirred at ambient temperature for 2 hours. A solution of 6-amino-4-(3-chloro-4-fluoroanilino)quinazoline (0.576 g) in DMA (5 ml) was added and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was purified by column chromatography using a 9:1:0.2 mixture of methylene chloride: methanol:

triethylamine as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(1,2,3-triazole-4-carboxamido)quinazoline (0.145 g);

NMR Spectrum: 7.43 (m, 1H), 7.82 (d, 1H), 7.95 (m, 1H), 8.18 (m, 2H), 8.43 (s, 1H), 8.58 (s, 1H), 8.88 (d, 1H), 9.89 (s, 1H), 10.55 (s, 1H);

Elemental Analysis: Found C, 55.6; H, 5.8; N, 21.4;

$C_{17}H_{11}ClFN_7O$ $0.8H_2O$ $1.1Et_3N$ requires C, 55.6; H, 5.7; N, 22.3%.

Example 24

3-Pyridinecarbonyl chloride hydrochloride salt (0.107 g) was added portionwise to a stirred mixture of 6-amino-4-(3-chloro-4-fluoroanilino)-7-methylaminoquinazoline (European Patent Application No. 0635507, within Example 3 thereof; 0.11 g), triethylamine (0.101 g) and DMA (1 ml). The mixture was heated to 100°C for 3 hours. The mixture was evaporated and the residue was purified by column chromatography using a C18 reversed-phase silica column and decreasingly polar mixtures of water and methanol (containing 0.2% trifluoroacetic acid) as eluent. The material so obtained was suspended in water and basified by the addition of an aqueous ammonium hydroxide solution. The resultant mixture was stirred at ambient temperature for 2 hours. The solid was isolated, washed with water and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-7-methylamino-6-(pyridine-3-carboxamido)quinazoline (0.061 g), m.p. >260°C;

NMR Spectrum: 2.83 (d, 3H), 6.41 (m, 1H), 6.7 (s, 1H), 7.38 (m, 1H), 7.6 (m, 1H), 7.84 (m, 1H), 8.19 (m, 1H), 8.29 (s, 1H), 8.42 (m, 1H), 8.48 (s, 1H), 8.79 (m, 1H), 9.24 (d, 1H), 9.5 (s, 1H);

Elemental Analysis: Found C, 55.1; H, 4.0; N, 18.4;

$C_{21}H_{16}ClFN_6O$ $2H_2O$ requires C, 54.9; H, 4.4; N, 18.3%.

Example 25

A mixture of 4-(3-chloro-4-fluoroanilino)-6-hydroxyquinazoline (0.87 g), 4-fluorobenzonitrile (0.423 g), potassium carbonate (0.828 g) and DMA (5 ml) was stirred and heated to 120°C for 4 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of methylene chloride and methanol. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(4-cyanophenoxy)quinazoline

(0.54 g);

NMR Spectrum: 7.21 (d, 2H), 7.43 (t, 1H), 7.72 (m, 1H), 7.82 (m, 1H), 7.88 (d, 2H), 7.93 (d, 1H), 8.18 (m, 1H), 8.39 (d, 1H), 8.68 (s, 1H);

Elemental Analysis: Found C, 63.9; H, 3.0; N, 14.1;

$C_{21}H_{12}ClFN_4O$ $0.2H_2O$ requires C, 64.0; H, 3.2; N, 14.2%.

The 4-(3-chloro-4-fluoroanilino)-6-hydroxyquinazoline used as a starting material was obtained as follows:-

A mixture of 6-acetoxy-4-chloroquinazoline (European Patent Application No. 0566226, Example 34, Note c; 54 g), 3-chloro-4-fluoroaniline (35.6 g) and isopropanol (850 ml) was stirred and heated to reflux for 90 minutes and then stored at ambient temperature for 16 hours. The precipitate was isolated and washed in turn with isopropanol and diethyl ether. There was thus obtained 6-acetoxy-4-(3-chloro-4-fluoroanilino)quinazoline (43.7 g, 49%).

A concentrated aqueous ammonium hydroxide solution (30% weight/volume, 35 ml) was added to a stirred mixture of 6-acetoxy-4-(3-chloro-4-fluoroanilino)quinazoline (22 g) and methanol (200 ml) and the mixture was heated to reflux for 3 hours. The mixture was evaporated and water (300 ml) was added to the residue. The solid was isolated, washed in turn with water (100 ml) and ethanol (60 ml) and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-hydroxyquinazoline (16.1 g, 93%);

NMR Spectrum: 7.43 (t, 1H), 7.45 (m, 1H), 7.70 (d, 1H), 7.78 (d, 1H), 7.88 (m, 1H), 8.24 (m, 1H), 8.5 (s, 1H), 9.6 (broad s, 1H), 10.1 (broad s, 1H).

Example 26

A mixture of 4-(3-chloro-4-fluoroanilino)-6-hydroxyquinazoline (5 g), 4-fluoronitrobenzene (2.67 g), potassium carbonate (4.74 g) and DMA (50 ml) was stirred and heated to 70°C for 10 minutes. The mixture was cooled to ambient temperature and then added dropwise to a stirred slurry of ice and water. The resultant precipitate was isolated, washed in turn with water, with a small volume of methanol and with diethyl ether and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(4-nitrophenoxy)quinazoline (6.8 g);

NMR Spectrum: 7.27 (d, 2H), 7.43 (t, 1H), 7.75 (m, 1H), 7.8 (m, 1H), 7.97 (d, 1H), 8.18 (m, 1H), 8.29 (d, 2H), 8.42 (d, 1H), 8.69 (s, 1H);

Elemental Analysis: Found C, 58.1; H, 2.8; N, 13.4;

$C_{20}H_{12}ClFN_4O_3$ requires C, 58.5; H, 2.9; N, 13.6%.

Example 27

A mixture of 4-(3-chloro-4-fluoroanilino)-6-(4-nitrophenoxy)quinazoline (6 g), 10% palladium-on-carbon catalyst (0.6 g) and DMA (250 ml) was stirred and heated to 60°C under an atmosphere of hydrogen for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using initially methylene chloride and then increasingly polar mixtures of methylene chloride and methanol as eluent. The product so obtained was triturated under methanol. There was thus obtained 6-(4-aminophenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline (2.3 g);

NMR Spectrum: 5.0 (broad s, 2H), 6.63 (d, 2H), 6.84 (d, 2H), 7.42 (t, 1H), 7.45 (m, 1H), 7.78 (d, 1H), 7.85 (m, 1H), 8.08 (d, 1H), 8.17 (m, 1H), 8.57 (s, 1H), 9.75 (s, 1H);

Elemental Analysis: Found C, 62.7; H, 3.8; N, 14.7;

$C_{20}H_{14}ClFN_4O$ requires C, 63.1; H, 3.7; N, 14.7%.

Example 28

tert-Butyl nitrite (0.243 g) was added to a stirred solution of 6-(4-aminophenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline (0.45 g) in DMF (25 ml) and the mixture was heated to 90°C for 3 hours. The mixture was cooled to ambient temperature and acidified by the addition of glacial acetic acid. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-phenoxyquinazoline (0.207 g);

NMR Spectrum: 7.0-7.3 (m, 5H), 7.32 (d, 1H), 7.35-7.6 (m, 3H), 7.9 (m, 1H), 7.93 (d, 1H), 8.73 (s, 1H);

Elemental Analysis: Found C, 62.6; H, 3.9; N, 11.5;

$C_{20}H_{13}ClFN_3O$ $1H_2O$ requires C, 62.6; H, 3.9; N, 11.5%.

Example 29

4-(3-Chloro-4-fluoroanilino)-6-(4-cyanophenoxy)quinazoline (2.7 g) was added portionwise to a stirred mixture of lithium aluminium hydride (1M in THF, 10 ml) and diethyl ether (50 ml). The resultant mixture was stirred at ambient temperature for 1 hour. Glacial acetic acid was added dropwise to destroy the excess of reducing agent. The mixture was partitioned between ethyl acetate and a dilute aqueous ammonium hydroxide solution. The

organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 6-(4-aminomethylphenoxy)-4-(3-chloro-4-fluoroanilino)-quinazoline (1.8 g);

NMR Spectrum: 3.23 (s, 2H), 3.8 (broad s, 2H), 7.18 (d, 2H), 7.43 (d, 2H), 7.47 (t, 1H), 7.6 (m, 1H), 7.86 (m, 1H), 7.9 (d, 1H), 8.22 (m, 1H), 8.31 (d, 1H), 8.65 (s, 1H);

Elemental Analysis: Found C, 61.0; H, 4.4; N, 13.3;

$C_{21}H_{16}ClFN_4O$ $1H_2O$ requires C, 61.1; H, 4.4; N, 13.6%.

Example 30

Di-(2-bromoethyl)ether (0.28 g) was added to a stirred mixture of 6-(4-aminomethylphenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline (0.5 g), potassium carbonate (0.33 g) and DMA (5 ml). The resultant mixture was stirred and heated to 70°C for 30 minutes. The mixture was evaporated and the residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-(4-morpholinomethylphenoxy)quinazoline (0.192 g);

NMR Spectrum: 2.37 (broad s, 4H), 3.49 (s, 2H), 3.62 (broad s, 4H), 7.02 (d, 2H), 7.34 (d, 2H), 7.41 (t, 1H), 7.58 (m, 1H), 7.82 (m, 2H), 8.2 (m, 2H), 8.62 (s, 1H), 9.79 (broad s, 1H);

Elemental Analysis: Found C, 63.4; H, 5.0; N, 12.0;

$C_{25}H_{22}ClFN_4O_2$ $0.5H_2O$ requires C, 63.4; H, 4.9; N, 11.8%.

Example 31

A mixture of 6-bromomethyl-4-(3-methylanilino)quinazoline (European Patent Application No. 0566226, Example 35 thereof; 0.3 g), imidazole (0.264 g) and ethanol (4 ml) was stirred at ambient temperature for 4 hours. The mixture was evaporated and the residue was purified on a C18 reversed-phase silica column using decreasingly polar mixtures of water and methanol, each containing 0.2% trifluoroacetic acid, as eluent. There was thus obtained 6-(1-imidazolylmethyl)-4-(3-methylanilino)quinazoline (0.27 g), m.p. 151-155°C;

NMR Spectrum: 2.37 (s, 3H), 5.66 (s, 2H), 7.07 (d, 1H), 7.36 (t, 1H), 7.53 (s, 1H), 7.58

(d, 1H), 7.74 (m, 1H), 7.8 (d, 1H), 7.88 (d, 1H), 7.97 (m, 1H), 8.69 (s, 1H), 8.79 (s, 1H), 9.26 (s, 1H), 10.78 (broad s, 1H);

Elemental Analysis: Found C, 49.1; H, 3.8; N, 12.2;

$C_{19}H_{17}N_5$ $2CF_3CO_2H$ $1H_2O$ requires C, 49.2; H, 3.7; N, 12.5%.

Example 32

A mixture of 4-(3-chloro-4-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (0.5 g), 2-chloromethylpyridine hydrochloride salt (0.282 g), potassium carbonate (1.5 g) and DMF (15 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature and poured into water. The precipitate was isolated and recrystallised from methanol. There was thus obtained 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(2-pyridylmethoxy)quinazoline (0.37 g);

NMR Spectrum: 3.98 (s, 3H), 5.35 (s, 2H), 7.26 (s, 1H), 7.4 (m, 2H), 7.64 (m, 1H), 7.8 (m, 1H), 7.9 (m, 1H), 8.01 (s, 1H), 8.15 (m, 1H), 8.51 (s, 1H), 8.62 (m, 1H), 9.56 (s, 1H);

Elemental Analysis: Found C, 61.1; H, 4.0; N, 13.5;

$C_{21}H_{16}ClFN_4O_2$ requires C. 61.4; H, 3.9; N, 13.6%.

The 4-(3-chloro-4-fluoroanilino)-6-hydroxy-7-methoxyquinazoline used as a starting material was obtained as follows:-

6,7-Dimethoxy-3.4-dihydroquinazolin-4-one (European Patent Application No. 0566226, Example 1 thereof; 26.5 g) was added portionwise to stirred methanesulphonic acid (175 ml). L-Methionine (22 g) was added and the resultant mixture was stirred and heated to reflux for 5 hours. The mixture was cooled to ambient temperature and poured onto a mixture (750 ml) of ice and water. The mixture was neutralised by the addition of a concentrated (40%) aqueous sodium hydroxide solution. The precipitate was isolated, washed with water and dried. There was thus obtained 6-hydroxy-7-methoxy-3,4-dihydroquinazolin-4-one (11.5 g).

After repetition of the previous reaction, a mixture of 6-hydroxy-7-methoxy-3,4-dihydroquinazolin-4-one (14.18 g), acetic anhydride (110 ml) and pyridine (14 ml) was stirred and heated to 100°C for 2 hours. The mixture was poured onto a mixture (200 ml) of ice and water. The precipitate was isolated, washed with water and dried. There was thus obtained 6-acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one (13 g, 75%);

NMR Spectrum: 2.3 (s, 3H), 3.8 (s, 3H), 7.3 (s, 1H), 7.8 (s, 1H), 8.1 (s, 1H), 12.2 (broad s, 1H).

After repetition of the previous steps, a mixture of 6-acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one (15 g), thionyl chloride (215 ml) and DMF (4.3 ml) was stirred and heated to 90°C for 4 hours. The mixture was cooled to ambient temperature and the thionyl chloride was evaporated. There was thus obtained 6-acetoxy-4-chloro-7-methoxyquinazoline hydrochloride salt which was used without further purification.

A mixture of the material so obtained, 3-chloro-4-fluoroaniline (9.33 g) and isopropanol (420 ml) was stirred and heated to 90°C for 5 hours. The mixture was cooled to ambient temperature and the precipitate was isolated, washed in turn with isopropanol and methanol and then dried. There was thus obtained 6-acetoxy-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline hydrochloride salt (14 g, 56%);

NMR Spectrum: 2.4 (s, 3H), 4.0 (s, 3H), 7.5 (t, 1H), 7.6 (s, 1H), 7.75 (m, 1H), 8.05 (m, 1H), 8.8 (s, 1H), 8.95 (s, 1H), 11.5 (broad s, 1H).

A concentrated aqueous ammonium hydroxide solution (30% weight/volume, 7.25 ml) was added to a stirred mixture of the material so obtained and methanol (520 ml). The mixture was stirred at ambient temperature for 17 hours and then heated to 100°C for 1.5 hours. The mixture was cooled and the precipitate was isolated and dried. There was thus obtained 4-(3-chloro-4-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (10.62 g, 95%), m.p. >270°C (decomposes);

NMR Spectrum: 4.0 (s, 3H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (s, 1H), 7.85 (m, 1H), 8.2 (m, 1H), 8.5 (s, 1H), 9.45 (s, 1H), 9.65 (s, 1H).

Example 33

Using an analogous procedure to that described in Example 32, 4-(3-chloro-4-fluoroanilino)-6-hydroxy-7-methoxyquinazoline was reacted with 3-chloromethylpyridine, hydrochloride salt to give 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-pyridylmethoxy)-quinazoline in 18% yield;

NMR Spectrum: 3.93 (s, 3H), 5.28 (s, 2H), 7.16 (s, 1H), 7.4 (m, 2H), 7.75 (m, 1H), 7.95 (m, 1H), 8.1 (m, 2H), 8.4 (s, 1H), 8.6 (m, 1H), 8.75 (m, 1H);

Elemental Analysis: Found C, 61.0; H, 3.9; N, 13.5;

$C_{21}H_{16}ClFN_4O_2$ requires C, 61.4; H, 3.9; N, 13.6%.

Example 34

A mixture of 6-bromomethyl-4-(3-methylanilino)quinazoline (0.3 g), 4-mercapto-1,2,3-triazole disodium salt (0.535 g) and DMF (3 ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was purified by column chromatography using a C18 reversed-phase silica column and a 1:1 mixture of methanol and water, each containing 0.2% trifluoroacetic acid, as eluent. There was thus obtained 4-(3-methylanilino)-6-(1,2,3-triazol-4-ylthiomethyl)quinazoline (0.22 g), m.p. 64-68°C;
NMR Spectrum: 2.38 (s, 3H), 4.36 (s, 2H), 7.15 (d, 1H), 7.38 (t, 1H), 7.49 (m, 2H), 7.83 (s, 1H), 8.0 (m, 1H), 8.58 (d, 1H), 8.87 (s, 1H), 11.2 (broad s, 1H);
Elemental Analysis: Found C, 47.5; H, 3.4; N, 16.0;
$C_{18}H_{16}N_6S$ 1.6CF_3CO_2H 0.25H_2O requires C, 47.6; H, 3.4; N, 15.7%.

Example 35

Using an analogous procedure to that described in Example 34, 6-bromomethyl-4-(3-methylanilino)quinazoline was reacted with 2-mercapto-1-methylimidazole sodium salt [prepared by the reaction of 2-mercapto-1-methylimidazole and sodium ethoxide in ethanol] to give 4-(3-methylanilino)-6-(N-methylimidazol-2-ylthiomethyl)quinazoline in 65% yield, m.p. 137-139°C;

NMR Spectrum: 2.42 (s, 3H), 3.6 (s, 3H), 4.48 (s, 2H), 6.97 (d, 1H), 7.13 (d, 1H), 7.39 (t, 1H), 7.55 (m, 2H), 7.6 (d, 1H), 7.83 (d, 1H), 7.93 (m, 1H), 8.5 (s, 1H), 8.83 (s, 1H), 10.9 (broad s, 1H);
Elemental Analysis: Found C, 48.3; H, 3.6; N, 11.6;
$C_{20}H_{19}N_5S$ 2CF_3CO_2H 0.5H_2O requires C, 48.1; H, 3.5; N, 11.7%.

Example 36

A mixture of 6-bromomethyl-4-(3-methylanilino)quinazoline (1.6 g), 2-mercaptoimidazole (0.316 g) and DMF (20 ml) was stirred and heated at 60°C for 6 hours. The mixture was cooled to ambient temperature and evaporated. The residue was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 6-(2-imidazolylthiomethyl)-4-(3-methylanilino)-quinazoline (0.43 g), m.p. 217-219°C;
NMR Spectrum: 2.33 (s, 3H), 4.45 (s, 2H), 6.97 (d, 1H), 7.12 (s, 2H), 7.29 (m, 1H), 7.64

(m, 2H), 7.72 (m, 2H), 8.47 (s, 1H), 8.57 (s, 1H);
Elemental Analysis: Found C, 65.8; H, 4.6; N, 19.9;
$C_{19}H_{17}N_5S$ requires C, 65.7; H, 4.9; N, 20.2%.

Example 37

Using an analogous procedure to that described in Example 34, 6-bromomethyl-4-(3-methylanilino)quinazoline was reacted with 2-mercaptobenzimidazole sodium salt to give 6-(2-benzimidazolylthiomethyl)-4-(3-methylanilino)quinazoline in 59% yield, m.p. 123-129°C;
NMR Spectrum: 2.34 (s, 3H), 4.77 (s, 2H), 6.96 (d, 1H), 7.13 (m, 2H), 7.28 (t, 1H), 7.46 (broad s, 2H), 7.68 (m, 3H), 7.96 (m, 1H), 8.57 (s, 1H), 8.65 (d, 1H), 9.79 (broad s, 1H);
Elemental Analysis: Found C, 64.9; H, 5.3; N, 15.9;
$C_{23}H_{19}N_5S$ 1.6H_2O 0.1CH_3OH requires C, 64.5; H, 5.3; N, 16.3%.

Example 38

Using an analogous procedure to that described in Example 5, 6-bromo-4-[3-methyl-4-(2-pyridylmethoxy)anilino]quinazoline dihydrochloride salt was reacted with di-isopropyl 2-thienylboronate to give 4-[3-methyl-4-(2-pyridylmethoxy)anilino]-6-(2-thienyl)-quinazoline in 70% yield, m.p. 205-206°C;
NMR Spectrum: 2.3 (s, 3H), 5.2 (s, 2H), 7.0 (d, 1H), 7.2 (m, 1H), 7.35 (m, 1H), 7.5 (m, 3H), 7.6 (m, 1H), 7.7 (m, 1H), 7.75 (d, 1H), 7.85 (m, 1H), 8.1 (m, 1H), 8.48 (s, 1H), 8.55 (m, 1H), 8.75 (d, 1H), 9.8 (broad s, 1H);
Elemental Analysis: Found C, 70.8; H, 4.7; N, 13.0;
$C_{25}H_{20}N_4OS$ requires C, 70.7; H, 4.75, N, 13.2%.

The 6-bromo-4-[3-methyl-4-(2-pyridylmethoxy)anilino]quinazoline dihydrochloride salt used as a starting material was obtained as follows:-

Sodium hydride (60% dispersion in mineral oil, 1.24 g) was added to a solution of 2-pyridylmethanol (2.49 ml) in NMP (100 ml) and the mixture was stirred at ambient temperature for 15 minutes. 2-Fluoro-5-nitrotoluene (4 g) was added and the mixture was heated to 140°C for 2.5 hours. The mixture was cooled to ambient temperature, poured into water (300 ml) and stirred for 30 minutes. The precipitate was isolated, washed with water and dried. The material so obtained was purified by column chromatography using

increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 5-nitro-2-tolyl 2-pyridylmethyl ether (1.61 g, 26%);

NMR Spectrum: 2.32 (s, 3H), 5.35 (s, 2H), 7.21 (d, 1H), 7.35 (m, 1H), 7.55 (d, 1H), 7.85 (m, 1H), 8.09 (m, 1H), 8.1 (s, 1H), 8.6 (m, 1H).

A mixture of 5-nitro-2-tolyl 2-pyridylmethyl ether (2 g), iron powder (1 g), concentrated hydrochloric acid (1 ml), water (2 ml) and ethanol (50 ml) was stirred and heated to reflux for 4 hours. The mixture was allowed to cool to ambient temperature, basified by the addition of 2M aqueous sodium hydroxide solution and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and evaporated. There was thus obtained 5-amino-2-tolyl 2-pyridylmethyl ether in 97% yield;

NMR Spectrum: 2.09 (s, 3H), 4.61 (s, 2H), 5.0 (s, 2H), 6.32 (m, 1H), 6.42 (d, 1H), 6.67 (d, 1H), 7.31 (m, 1H), 7.50 (d, 1H), 7.81 (m, 1H), 8.54 (m, 1H).

Using an analogous procedure to that described in the third paragraph of the portion of Example 1 which is concerned with the preparation of starting materials, except that the product was recrystallised from a mixture of methanol and ethanol, 6-bromo-4-chloroquinazoline was reacted with 5-amino-2-tolyl 2-pyridylmethyl ether to give 6-bromo-4-[3-methyl-4-(2-pyridylmethoxy)anilino)quinazoline dihydrochloride salt in 68% yield, m.p. 232-234°C;

NMR Spectrum: 2.3 (s, 3H), 5.35 (s, 2H), 7.13 (m, 1H), 7.52 (m, 3H), 7.63 (d, 1H), 7.9 (d, 1H), 8.08 (m, 1H), 8.25 (m, 1H), 8.7 (m, 1H), 8.92 (s, 1H), 9.17 (d, 1H), 11.62 (d, 1H);

Elemental Analysis: Found C, 48.4; H, 4.2; N, 10.6;

$C_{21}H_{17}BrN_4O$ 2HCl 1.5H_2O requires C, 48.4; H, 4.25; N, 10.7%.

Example 39

Using an analogous procedure to that described in Example 5, 6-bromo-4-[3-methyl-4-(2-pyridylmethoxy)anilino]quinazoline dihydrochloride salt was reacted with di-isopropyl 3-furylboronate to give 6-(3-furyl)-4-[3-methyl-4-(2-pyridylmethoxy)anilino]-quinazoline in 55% yield. m.p. 206-208°C;

NMR Spectrum: 2.32 (s, 3H), 5.22 (s, 2H), 7.05 (d, 1H), 7.15 (d, 1H), 7.36 (m, 1H), 7.55 (m, 3H), 7.75 (d, 1H), 7.87 (m, 2H), 8.1 (m, 2H), 8.33 (d, 1H), 8.48 (s, 1H), 8.6 (m, 1H), 8.69 (d, 1H), 9.62 (s, 1H);

Elemental Analysis: Found C, 73.2; H, 4.9; N, 13.6;

$C_{25}H_{20}N_4O_2$ requires C, 73.5; H, 4.9; N, 13.7%.

The di-isopropyl 3-furylboronate used as a starting material was obtained as follows:-

n-Butyllithium (1.6M in hexane, 1 ml) was added dropwise to a stirred mixture of 3-bromofuran (0.21 g), tri-isopropyl borate (0.4 ml) and THF (5 ml) which had been cooled to -78°C. The mixture was stirred and allowed to warm to ambient temperature. The mixture was evaporated to give the required starting material which was used without further purification.

Example 40

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone	2.25
	Magnesium stearate	3.0

(c) Tablet III

	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d) Capsule

	mg/capsule
Compound X	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

(e) Injection I

	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% w/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f) Injection II

	(10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III

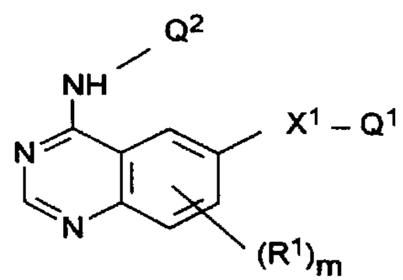
	(1mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

<u>Note</u>

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A quinazoline derivative of the formula I



I

wherein X^1 is a direct link or a group of the formula CO, $C(R^2)_2$, $CH(OR^2)$, $C(R^2)_2$-$C(R^2)_2$, $C(R^2)$=$C(R^2)$, C≡C, CH(CN), O, S, SO, SO_2, $N(R^2)$, $CON(R^2)$, $SO_2N(R^2)$, $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)$, $SC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2O$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$, and each R^2 is independently hydrogen or (1-4C)alkyl;

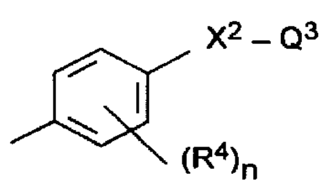
wherein Q^1 is phenyl, naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and Q^1 optionally bears up to 3 substituents selected from halogeno, hydroxy, amino, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-3C)alkylenedioxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(1-4C)alkylpiperazin-1-yl, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl, 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl, halogeno-(2-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-4C)alkoxy-(2-4C)alkoxy, amino-(2-4C)alkoxy, (1-4C)alkylamino-(2-4C)alkoxy, di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, (1-4C)alkylthio-(2-4C)alkoxy, (1-4C)alkylsulphinyl-(2-4C)alkoxy, (1-4C)alkylsulphonyl-(2-4C)alkoxy, halogeno-(2-4C)alkylamino, hydroxy-(2-4C)alkylamino,

(1-4C)alkoxy-(2-4C)alkylamino, amino-(2-4C)alkylamino, (1-4C)alkylamino-(2-4C)alkylamino, di-[(1-4C)alkyl]amino-(2-4C)alkylamino, pyrrolidin-1-yl-(2-4C)alkylamino, piperidino-(2-4C)alkylamino, morpholino-(2-4C)alkylamino, piperazin-1-yl-(2-4C)alkylamino, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkylamino, N-(1-4C)alkyl-halogeno-(2-4C)alkylamino, N-(1-4C)alkyl-hydroxy-(2-4C)alkylamino, N-(1-4C)alkyl-(1-4C)alkoxy-(2-4C)alkylamino, halogeno-(2-4C)alkanoylamino, hydroxy-(2-4C)alkanoylamino, (1-4C)alkoxy-(2-4C)alkanoylamino, (3-4C)alkenoylamino, (3-4C)alkynoylamino, amino-(2-4C)alkanoylamino, (1-4C)alkylamino-(2-4C)alkanoylamino, di-[(1-4C)alkyl]amino-(2-4C)alkanoylamino, pyrrolidin-1-yl-(2-4C)alkanoylamino, piperidino-(2-4C)alkanoylamino, morpholino-(2-4C)alkanoylamino, piperazin-1-yl-(2-4C)alkanoylamino and 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkanoylamino, and wherein any of the above-mentioned substituents comprising a CH_2 (methylene) group which is not attached to a halogeno, SO or SO_2 group or to a N, O or S atom optionally bears on said CH_2 group a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

wherein m is 1 or 2 and each R^1 is independently hydrogen, halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-4C)alkoxycarbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl or N,N-di-[(1-4C)alkyl]carbamoyl;

and wherein Q^2 is phenyl or a 9- or 10-membered bicyclic heterocyclic moiety containing 1 or 2 nitrogen heteroatoms and optionally containing a further heteroatom selected from oxygen, nitrogen and sulphur, and Q^2 optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-(1-4C)alkylcarbamoyl,

or Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula CO, $C(R^3)_2$, $CH(OR^3)$, $C(R^3)_2$-$C(R^3)_2$, $C(R^3)$=$C(R^3)$,

C≡C, CH(CN), O, S, SO, SO_2, $N(R^3)$, $CON(R^3)$, $SO_2N(R^3)$, $N(R^3)CO$, $N(R^3)SO_2$, $OC(R^3)_2$, $SC(R^3)_2$, $C(R^3)_2O$ or $C(R^3)_2S$ wherein each R^3 is independently hydrogen or (1-4C)alkyl, Q^3 is phenyl or naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heteroaryl moiety is a single ring or is fused to a benzo ring, and wherein said phenyl or naphthyl group or heteroaryl moiety optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-[(1-4C)alkyl]carbamoyl,

n is 1, 2 or 3 and each R^4 is independently hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino or (2-4C)alkanoylamino;

or a pharmaceutically-acceptable salt thereof;

provided that, when Q^1 is optionally-substituted phenyl, X^1 is not $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$; and when X^1 is a direct link, Q^1 is not a 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to 3 nitrogen heteroatoms.

2. A quinazoline derivative of the formula I as claimed in claim 1 wherein X^1 is a direct link or a group of the formula CO, $C(R^2)_2$, $CH(OR^2)$, $C(R^2)_2$-$C(R^2)_2$, $C(R^2)$=$C(R^2)$, C≡C, CH(CN), O, S, SO, SO_2, $N(R^2)$, $CON(R^2)$, $SO_2N(R^2)$, $N(R^2)CO$, $N(R^2)SO_2$, $OC(R^2)_2$, $SC(R^2)_2$, $N(R^2)C(R^2)_2$, $C(R^2)_2O$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$, and each R^2 is independently hydrogen or (1-4C)alkyl;

wherein Q^1 is a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and Q^1 optionally bears up to 3 substituents selected from halogeno, hydroxy, amino, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-3C)alkylenedioxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(1-4C)alkylpiperazin-1-yl, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl,

piperazin-1-yl-(1-4C)alkyl, 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl, halogeno-(2-4C)alkoxy, hydroxy-(2-4C)alkoxy, (1-4C)alkoxy-(2-4C)alkoxy, amino-(2-4C)alkoxy, (1-4C)alkylamino-(2-4C)alkoxy, di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, (1-4C)alkylthio-(2-4C)alkoxy, (1-4C)alkylsulphinyl-(2-4C)alkoxy, (1-4C)alkylsulphonyl-(2-4C)alkoxy, halogeno-(2-4C)alkylamino, hydroxy-(2-4C)alkylamino, (1-4C)alkoxy-(2-4C)alkylamino, amino-(2-4C)alkylamino, (1-4C)alkylamino-(2-4C)alkylamino, di-[(1-4C)alkyl]amino-(2-4C)alkylamino, pyrrolidin-1-yl-(2-4C)alkylamino, piperidino-(2-4C)alkylamino, morpholino-(2-4C)alkylamino, piperazin-1-yl-(2-4C)alkylamino, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkylamino, N-(1-4C)alkyl-halogeno-(2-4C)alkylamino, N-(1-4C)alkyl-hydroxy-(2-4C)alkylamino, N-(1-4C)alkyl-(1-4C)alkoxy-(2-4C)alkylamino, halogeno-(2-4C)alkanoylamino, hydroxy-(2-4C)alkanoylamino, (1-4C)alkoxy-(2-4C)alkanoylamino, (3-4C)alkenoylamino, (3-4C)alkynoylamino, amino-(2-4C)alkanoylamino, (1-4C)alkylamino-(2-4C)alkanoylamino, di-[(1-4C)alkyl]amino-(2-4C)alkanoylamino, pyrrolidin-1-yl-(2-4C)alkanoylamino, piperidino-(2-4C)alkanoylamino, morpholino-(2-4C)alkanoylamino, piperazin-1-yl-(2-4C)alkanoylamino and 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkanoylamino, and wherein any of the above-mentioned substituents comprising a CH_2 (methylene) group which is not attached to a halogeno, SO or SO_2 group or to a N, O or S atom optionally bears on said CH_2 group a substituent selected from hydroxy, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkyl]amino;

wherein m is 1 or 2 and each R^1 is independently hydrogen, halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-4C)alkoxycarbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl or N,N-di-[(1-4C)alkyl]carbamoyl;

and wherein Q^2 is phenyl which optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-(1-4C)alkylcarbamoyl;

or a pharmaceutically-acceptable salt thereof;

provided that, when X^1 is a direct link, Q^1 is not a 5- or 9-membered nitrogen-linked heteroaryl moiety containing up to 3 nitrogen heteroatoms.

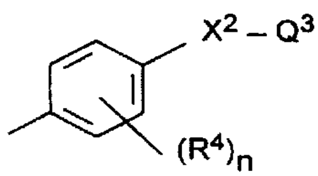
3. A quinazoline derivative of the formula I as claimed in claim 1 wherein X^1 is a direct link or a group of the formula CH_2, CH_2CH_2, NH, NHCO, $NHSO_2$, OCH_2, SCH_2, $NHCH_2$, CH_2O or CH_2S;

Q^1 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-isoxazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, 2-thiazolyl, 4-thiazolyl, 5-isothiazolyl or 1,2,3-triazol-4-yl which optionally bears a substituent selected from methyl, aminomethyl, 2-aminoethyl, methylaminomethyl, 2-methylaminoethyl, dimethylaminomethyl, 2-dimethylaminoethyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, piperidinomethyl, 2-piperidinoethyl, morpholinomethyl, 2-morpholinoethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 4-methylpiperazin-1-ylmethyl and 2-(4-methylpiperazin-1-yl)ethyl;

m is 1 and R^1 is hydrogen or methoxy;

and Q^2 is phenyl which optionally bears 1, 2 or 3 substituents selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl and methoxy,

or Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula CO or OCH_2, Q^3 is phenyl or 2-pyridyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo, methyl and methoxy, n is 1 and R^4 is hydrogen, fluoro, chloro, bromo or methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

4. A quinazoline derivative of the formula I as claimed in claim 1 wherein X^1 is a direct link or a group of the formula NHCO, OCH_2 or $NHCH_2$;

Q^1 is 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-oxazolyl, 5-isoxazolyl or 4-imidazolyl which optionally bears a substituent selected from aminomethyl, morpholinomethyl and 2-morpholinoethyl;

m is 1 and R^1 is hydrogen or methoxy;

and Q^2 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo and methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

5. The quinazoline derivative of the formula I as claimed in claim 1 selected from:-

4-(3-chloro-4-fluoroanilino)-6-(3-furyl)quinazoline,

4-(3-chloro-4-fluoroanilino)-6-(2-thienyl)quinazoline,

4-(3-chloro-4-fluoroanilino)-6-[5-(2-morpholinoethyl)thien-2-yl]quinazoline,

4-(3-chloro-4-fluoroanilino)-6-(5-morpholinomethylthien-3-yl)quinazoline and

4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-pyridylmethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

6. A quinazoline derivative of the formula I as claimed in claim 1:

wherein X^1 is a direct link;

Q^1 is thienyl which bears a substituent selected from amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, pyrrolidin-1-yl-(1-4C)alkyl, piperidino-(1-4C)alkyl, morpholino-(1-4C)alkyl, piperazin-1-yl-(1-4C)alkyl and 4-(1-4C)alkylpiperazin-1-yl-(1-4C)alkyl;

m is 1 and R^1 is hydrogen;

and Q^2 is phenyl which optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-(1-4C)alkylcarbamoyl;

or a pharmaceutically-acceptable salt thereof.

7. A quinazoline derivative of the formula I as claimed in claim 1

wherein X^1 is a direct link;

Q^1 is 2-thienyl which optionally bears a substituent selected from methyl, aminomethyl, 2-aminoethyl, methylaminomethyl, 2-methylaminoethyl, dimethylaminomethyl, 2-dimethylaminoethyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, piperidinomethyl, 2-piperidinoethyl, morpholinomethyl, 2-morpholinoethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 4-methylpiperazin-1-ylmethyl and 2-(4-methylpiperazin-1-yl)ethyl;

m is 1 and R^1 is hydrogen or methoxy;

and Q^2 is phenyl which optionally bears 1, 2 or 3 substituents selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl and methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

8. A quinazoline derivative of the formula I as claimed in claim 1 wherein X^1 is a direct link;

Q^1 is 2-thienyl which optionally bears a substituent selected from aminomethyl, morpholinomethyl and 2-morpholinoethyl;

m is 1 and R^1 is hydrogen or methoxy;

and Q^2 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo and methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

9. The quinazoline derivative of the formula I as claimed in claim 1:-

4-(3-chloro-4-fluoroanilino)-6-[5-(2-morpholinoethyl)thien-2-yl]quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

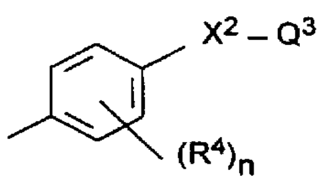
10. A quinazoline derivative of the formula I as claimed in claim 1 wherein X^1 is a direct link or a group of the formula O;

Q^1 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo, amino, cyano, nitro, aminomethyl, methylaminomethyl, dimethylaminomethyl, diethylaminomethyl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl;

m is 1 and R^1 is hydrogen or methoxy; and

Q^2 is phenyl which optionally bears 1, 2 or 3 substituents selected from fluoro, chloro, bromo, trifluoromethyl, cyano, methyl and methoxy,

or Q^2 is a group of the formula II



II

wherein X^2 is a group of the formula OCH_2, Q^3 is 2-pyridyl, n is 1 and R^4 is hydrogen, fluoro, chloro or methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

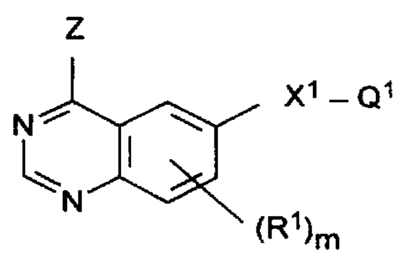
11. A quinazoline derivative of the formula I as claimed in claim 1 wherein X^1 is a direct link or a group of the formula O;

Q^1 is phenyl which optionally bears 1 or 2 substituents selected from amino, aminomethyl, diethylaminomethyl, pyrrolidin-1-ylmethyl, piperidinomethyl and morpholinomethyl;
m is 1 and R^1 is hydrogen; and
Q^2 is phenyl which optionally bears 1 or 2 substituents selected from fluoro, chloro and methyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

12. The quinazoline derivative of the formula I as claimed in claim 1 selected from:-
4-(3-methylanilino)-6-phenylquinazoline,
6-(4-aminomethylphenyl)-4-(3-chloro-4-fluoroanilino)quinazoline,
6-(4-aminophenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline,
6-(4-aminomethylphenoxy)-4-(3-chloro-4-fluoroanilino)quinazoline or
4-(3-chloro-4-fluoroanilino)-6-(4-morpholinomethylphenoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

13. A process for the preparation of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 12 which comprises:-

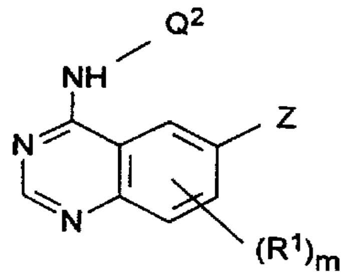
(a) the reaction of a quinazoline of the formula III



III

wherein Z is a displaceable group, with an aniline of the formula Q^2-NH_2;

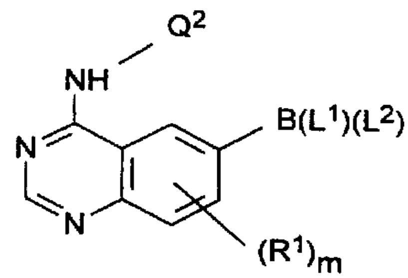
(b) for the preparation of those compounds of the formula I wherein X^1 is a direct link, the reaction of a quinazoline of the formula IV



IV

wherein Z is a displaceable group, with an organoboron reagent of the formula Q^1-$B(L^1)(L^2)$ wherein each L^1 and L^2, which may be the same or different, is a suitable ligand;

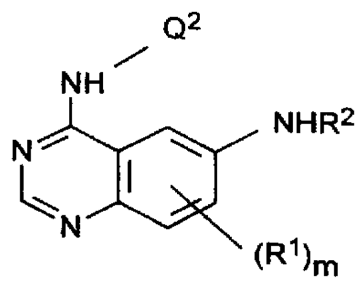
(c) for the preparation of those compounds of the formula I wherein X^1 is a direct link, the reaction of a quinazoline of the formula V



V

wherein each of L^1 and L^2, which may be the same or different, is a suitable ligand, with a compound of the formula Q^1-Z wherein Z is a displaceable group;

(d) for the production of those compounds of the formula I wherein X^1 is a group of the formula $N(R^2)CO$ or $N(R^2)SO_2$, the acylation of an amine of the formula VI

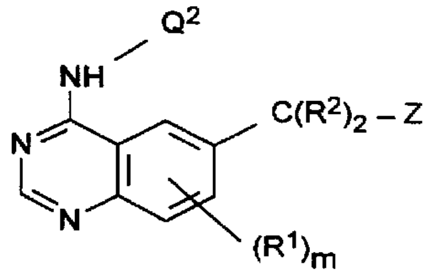


VI

with a carboxylic acid of the formula Q^1-CO_2H, or a reactive derivative thereof, or a sulphonic acid of the formula Q^1-SO_2OH, or a reactive derivative thereof, as appropriate;

(e) for the production of those compounds of the formula I wherein X^1 is a group of the formula $OC(R^2)_2$, $SC(R^2)_2$ or $N(R^2)C(R^2)_2$, the alkylation of an appropriate phenol, thiophenol or aniline with an alkylating agent of the formula Z-$C(R^2)_2$-Q^1 wherein Z is a displaceable group;

(f) for the production of those compound of the formula I wherein X^1 is a group of the formula $C(R^2)_2O$, $C(R^2)_2S$ or $C(R^2)_2N(R^2)$, the alkylation of the appropriate phenol of the formula HO-Q^1, thiophenol of the formula HS-Q^1 or aniline of the formula R^2NH-Q^1, with an alkylating agent of the formula VII



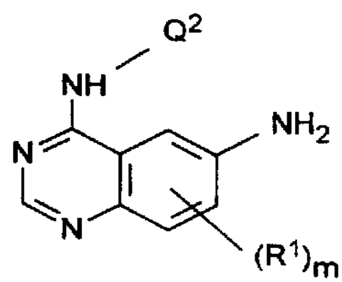
VII

wherein Z is a displaceable group;

(g) for the production of those compounds of the formula I which possess an aminomethyl substituent or wherein X^1 is a group of the formula $N(R^2)CH_2$ or $CH_2N(R^2)$, the reduction of a compound of the formula I which possesses a cyano substituent or wherein X^1 is a group of the formula $N(R^2)CO$ or $CON(R^2)$ as appropriate;

(h) for the production of those compounds of the formula I which possess an amino substituent, the reduction of a compound of the formula I which possesses a nitro substituent;

(i) for the production of those compounds of the formula I wherein X^1 is a group of the formula $NHCH(R^2)$, the reductive amination of a keto compound of the formula R^2-CO-Q^1 with an amine of the formula VIII



VIII

or (j) for the production of those compounds of the formula I wherein X^1 is a group of the formula O, S or $N(R^2)$, the coupling of an appropriate phenol, thiophenol or aniline with a compound of the formula Z-Q^1 wherein Z is a displaceable group;

and when a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required it may be obtained by reaction of said compound using a conventional procedure.

14. A pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 12 in association with a pharmaceutically-acceptable diluent or carrier.

15. The use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 12 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00344

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D239/94 A61K31/505 C07D401/04 C07D403/04 C07D405/04
C07D407/04 C07D409/04 C07D411/04 C07D413/14 C07D409/12
C07D411/12 C07D403/12 C07D401/12 C07D407/12 C07D409/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 566 226 A (ZENECA LIMITED) 20 October 1993 cited in the application * entire document * see claims 1-12	1-15
P,Y	WO 96 16960 A (ZENECA LIMITED) 6 June 1996 cited in the application see claims 1-10	1-15
Y	EP 0 635 498 A (ZENECA LIMITED) 25 January 1995 cited in the application see claims 1-12	1-15
Y	EP 0 602 851 A (ZENECA LIMITED) 22 June 1994 see claims 1-10	1-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 1997	29.05.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

INTERNATIONAL SEARCH REPORT

Intern ...al Application No
PCT/GB 97/00344

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 520 722 A (IMPERIAL CHEMICAL INDUSTRIES PLC) 30 December 1992 see claims 1-9 ---	1-15
Y	EP 0 635 507 A (ZENECA LIMITED) 25 January 1995 see claims 1-11 ---	1-15
Y	WO 92 20642 A (RHONE-POULENC RORER INTERNATIONAL) 26 November 1992 see claims 1-32 -----	1-15

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/GB 97/00344

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 566226 A	20-10-93	AT 130000 T	15-11-95
		AU 661533 B	27-07-95
		AU 3101093 A	22-07-93
		CA 2086968 A	21-07-93
		DE 69300754 D	14-12-95
		DE 69300754 T	28-03-96
		ES 2078798 T	16-12-95
		HU 9500185 A	28-07-95
		NZ 245662 A	26-09-95
		SK 1693 A	09-09-93
		US 5457105 A	10-10-95
		US 5616582 A	01-04-97
		ZA 9300015 A	20-07-93
		JP 6073025 A	15-03-94
WO 9616960 A	06-06-96	AU 3933095 A	19-06-96
EP 635498 A	25-01-95	AU 7191694 A	20-02-95
		WO 9503283 A	02-02-95
		JP 9500636 T	21-01-97
		US 5475001 A	12-12-95
		ZA 9405156 A	19-01-95
EP 602851 A	22-06-94	AT 143956 T	15-10-96
		AU 664496 B	16-11-95
		AU 5072893 A	23-06-94
		CA 2103383 A	11-06-94
		CN 1094043 A	26-10-94
		CZ 9302651 A	15-06-94
		DE 69305310 D	14-11-96
		DE 69305310 T	13-02-97
		ES 2093367 T	16-12-96
		FI 935431 A	11-06-94
		HU 65622 A	28-07-94
		JP 6336481 A	06-12-94
		NO 934504 A	13-06-94
		NZ 250218 A	25-06-96
		US 5580870 A	03-12-96
		ZA 9308594 A	10-06-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/00344

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 520722 A	30-12-92	AT 146781 T	15-01-97
		AU 651215 B	14-07-94
		AU 1842292 A	07-01-93
		CA 2071087 A	29-12-92
		DE 69216158 D	06-02-97
		DE 69216158 T	10-04-97
		JP 5208911 A	20-08-93
		NO 180105 B	11-11-96
		NZ 243082 A	24-02-95
		SK 182792 A	09-08-95
EP 635507 A	25-01-95	CA 2127411 A	20-01-95
		JP 7053556 A	28-02-95
		US 5569658 A	29-10-96
WO 9220642 A	26-11-92	AU 658646 B	27-04-95
		AU 1993492 A	30-12-92
		CA 2102780 A	11-11-92
		EP 0584222 A	02-03-94
		JP 6507643 T	01-09-94
		US 5409930 A	25-04-95
		US 5480883 A	02-01-96